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19 Perinatal Diseases

Introduction

This chapter considers the principles of the diseases that occur during the first month of life in animals born alive at term. Diseases causing abortion and stillbirth are not included. The specific diseases discussed are presented separately under their own headings.

The inclusion of a chapter on diseases of the newborn, and at this point in the book, needs explanation. The need for the chapter arises out of the special sensitivities that newborns have:

- Their immunologic incompetence
- Their dependence on adequate colostrum containing adequate antibodies at the right time
- Their dependence on frequent intake of readily available carbohydrate to maintain energy
- Their relative inefficiency in maintaining normal body temperature, upward or downward

All of these points require emphasis before proceeding to the study of each of the body systems.

There are no particular aspects of a clinical examination that pertain only to or mostly to neonates. The same clinical examination as is applied to adults is used, with additional, careful examination for congenital defects and diseases, which may involve the umbilicus, the liver, the heart valves, the joints and tendon sheaths, the eyes, and the meninges, and for birth-related trauma (e.g., rib fracture, joint luxation, distal limb fracture).

Because there is a much greater susceptibility to infectious disease, dehydration, and death, diagnosis and treatment must be reasonably accurate and rapid. Supportive therapy in the form of fluids, electrolytes and energy, and nursing care are especially important in the newborn to maintain homeostasis.

Perinatal and Postnatal Diseases

One of the difficulties in the study of perinatal and postnatal diseases is the variation in the type of age classification that occurs between publications, which makes it difficult to compare results and assessments. The term *perinatal* is usually used to describe morbidity or mortality that occurs at birth and in the first 24 hours of life. The term *neonatal* is usually used to describe morbidity or mortality between birth and 14 days. However, there is variation in the use of these terms. To ensure that our meanings are clear, we set out in the following section what we think is the most satisfactory classification of all the diseases of the fetus and the newborn, which is adapted from a scheme proposed for lambs. The importance of this type of classification is in the assessment of risk for a given type of disease and in the prediction of likely causes that should be investigated by further examinations. This approach is not of major importance in the assessment of disease in an individual animal, although it is of importance in helping establish the priority in diagnostic rule-outs. The classification is, however, of considerable value in the approach to perinatal morbidity and mortality in large flocks or herds, where an assessment of the age occurrence of morbidity and mortality can guide subsequent examinations to the probable group of cases, with optimal expenditure of investigative capital.

GENERAL CLASSIFICATION

FETAL DISEASES

Fetal diseases are diseases of the fetus during intrauterine life, for example, prolonged gestation, intrauterine infections, abortion, fetal death with resorption or mummification, and goiter.

PARTURIENT DISEASES

Parturient diseases are diseases associated with dystocia, causing cerebral anoxia or fetal hypoxemia, and their consequences and predispositions to other diseases; injury to the skeleton or soft tissues and maladjustment syndrome of foals are also included here.

POSTNATAL DISEASES

Postnatal diseases are divided into early, delayed, and late types:

- **Early postnatal disease** (within 48 hours of birth). Deaths that occur during this period are unlikely to be caused by an infectious disease unless it has been acquired congenitally. Most diseases occurring in this period are noninfectious and metabolic (e.g., hypoglycemia and hypothermia as a result of poor mothering, hypothermia as a result of exposure to cold, low vigor in neonates as a result of malnutrition). Congenital disease will commonly manifest during this period but may sometimes manifest later. Infectious diseases are often initiated during this period, but most manifest clinically at a later age because of their incubation period; some (e.g., navel infection, septicemic disease, and enterotoxigenic colibacillosis) have a short enough incubation to occur during this period.
- **Delayed postnatal disease** (2 to 7 days of age). Included in this category are desertion by the mother, mammary incompetence resulting in starvation, and diseases associated with increased susceptibility to infection as a result of failure in the transfer of colostral immunoglobulins (the predisposing causes to these occur in the first 12 to 24 hours of life). Examples include colibacillosis, joint ill, lamb dysentery, septicemic disease, and most of the viral enteric infections in young animals (e.g., rotavirus and coronavirus).
- **Late postnatal disease** (1 to 4 weeks of age). There is still some influence of hypogammaglobulinemia, with late-onset enteric diseases and the development and severity of respiratory disease in this period, but other diseases not directly associated with failure of transfer of immunoglobulins, such as cryptosporidiosis, white muscle disease, and enterotoxemia, start to become important.

PERINATAL DISEASE—GENERAL EPIDEMIOLOGY

Diseases of the newborn and neonatal mortality are a major cause of economic loss in livestock production. In cattle, sheep, and pigs, the national average perinatal mortalities exceed by far the perinatal mortality experienced in herds and flocks with good management. In these species the identification of the management deficiencies that are the cause of a higher-than-acceptable mortality in a herd or a flock is a most important long-term responsibility of the practicing veterinarian and, in most instances, is more important than the identification of the causal agent or the short-term treatment of individual animals with neonatal disease. In contrast, in horses, the individual is of extreme importance, and the primary thrust is in the treatment of neonatal disease.

All animals must be born close to term if they are to survive in a normal farm environment. Minimal gestational ages for viability (in days) for each of the species are as follows:

- Calf—240
- Foal—311
- Lamb—138
- Piglet—108
- Cria—295

LAMBS

Mortality Rates

Neonatal lamb mortality is one of the major factors in impairment of productivity in sheep-raising enterprises around the world, and nearly half of all preweaning lamb deaths occur on the day of birth.[1] Mortality can obviously vary with the management system (intensive versus extensive lambing, highly supervised versus minimally supervised, variations in the provision of shelter, etc.) and according to whether there is a particular disease problem in a given flock. Nonselective mortality surveys have shown population mortality rates in lambs, from birth to weaning, that vary from 10% to 30%, and there are flocks that may exceed this upper figure in the face of a major problem. In well-managed flocks, neonatal mortality is less than 10% and in some is below 5%.

Major Causes

The major cause of neonatal mortality in lambs is noninfectious disease. Many studies have explored the causes for neonatal lamb mortality, which are broadly categorized as follows:[2]

- Death related to birth process
- Failure of neonatal adaptation to postnatal life
- Infectious disease
- Functional disorders
- Predation

Fetal Disease

Infectious abortion can cause considerable fetal, parturient, and postnatal mortality in infected flocks, but it is a relatively minor cause of perinatal mortality overall. In contrast to other large animal species, abortion storms in sheep are often accompanied by significant mortality in liveborn animals. Many agents associated with abortion in ewes produce placentitis and cause abortion in late pregnancy. This frequently results in the birth of liveborn growth-retarded and weak lambs that die during the first few days of life. Any investigation of perinatal mortality in sheep should also consider the presence of agents causing abortion, although abortion and the birth of dead lambs is always prominent in abortion outbreaks.

Parturient Disease

Stillbirth occurs largely as a result of prolonged birth and fetal hypoxemia. Prolonged birth and dystocia are particular problems in large single lambs. Higher rates of stillbirth can also occur in flocks that are in poor condition. Prolonged birth is a major risk factor for subsequent postnatal disease.

Postnatal Disease

Starvation and hypothermia are common causes of death of neonatal lambs that can result from decreased vigor, pain or trauma after a difficult delivery, failure to adapt to postnatal life, or infectious disease. A number of studies have consistently identified **low birth weight** as the single most important factor associated with lamb mortality.[1,2] Other common factors associated with the mortality rates of neonatal lambs are litter size (which cannot entirely be attributed to lower birth weight of twins), lamb sex (with males having higher mortality than females), and lamb behavior.[1] Management practices that have been found to reduce lamb mortality include winter feeding of pregnant ewes and housing at lambing.[2]

Birth Weight

Birth weight is determined by the nutrition and genetics of the ewe and by litter size, which is also determined by the parity and genetics of the ewe. Reflecting these influences, most surveys of neonatal mortality in lambs show the following characteristics:

- A significant association between the body condition score or **nutrition of the late pregnant ewe** and perinatal mortality
- A relation between **birth weight** and mortality (depending on the breed, a birth weight of less than 2.5 to 3.0 kg has increased risk for death)
- A higher mortality in lambs from **primiparous ewes**[1]
- A pronounced effect of **litter size**, with mortality in lambs born as triplets being higher than in those born as twins, which in turn is higher than that in lambs born as singles

Lambs with low birth weight are born with fewer body reserves, are less vigorous at birth, and take longer to stand (and thus to reach the teat and ingest colostrum). They are also more susceptible to hypothermia because of higher body surface relative to body mass, lower body fat content, and lower thermogenic capacity as a result of lower muscle mass.

The association between birth weight and lamb mortality has a U-shaped pattern, with the lowest mortality rates with normal birth weight and increasing mortality rates with both decreasing and increasing birth weight. An increase in mortality in large-birth-weight lambs born as singles has been associated with increased risk for dystocia.

Environmental Factors

Environmental factors of temperature, wetness, and wind can greatly affect lamb mortality rates; their influence varies according to the management system.

The identification of the determinants of mortality just described is of more than academic value because almost all can be modulated by the identification of **at-risk groups** and the adjustment of management procedures or by the identification and mitigation of adverse environmental factors.

Infectious Disease

Infectious disease can be important in some flocks but commonly contributes to lamb mortality from 2 days of age on. The major infectious diseases of lambs that cause mortality are enteritis and pneumonia. Their prevalence varies with the management system—enteric disease and liver abscess are more common in shed lambing systems than with lambing at pasture. Risk for pneumonia is greatest in very light or heavy lambs and in lambs from maiden ewes and ewes with poor milk production.

Other Factors

Other factors can be important in individual flocks or regions. Lambs found dead or missing may account for significant losses in some conditions, such as mountain or hill pastures. **Predation**, or predation injury, is an important cause of loss in some areas of the world and, depending on the region, can occur from domestic dogs, coyotes, birds, or feral pigs. **Poor mothering** and an inability of the ewe to gather and bond to both lambs in the case of twins can be a problem in Merinos and can cause permanent separation of lambs from the ewe and subsequent death from starvation.

Management at lambing can also influence the patterns of mortality. Intensive stocking at the time of lambing allows increased periparturient supervision and tends to reduce the incidence of stillbirths and lamb mortality related to parturition. It can furthermore ensure the early feeding of colostrum to weak lambs. On the other hand, it can result in a greater occurrence of mismothering associated with the activities of "robber" ewes and may increase lamb mortality related to infectious disease.[3] Mortality rates can differ between breeds, and lambs from crossbred dams may have higher survival rates.

Recording Systems

Simple systems for recording, determining, and evaluating the major causes of lamb mortality in a flock, for determining the time of death in relation to birth, and for relating the deaths to the weather and management system are available. These systems of examination are effective in revealing the extent of lamb losses and the areas of management that require improvement, and they are much more cost-effective than extensive laboratory examinations, which may give little information on the basic cause of the mortality. More intensive examination systems that combine these simple examinations with selected biochemical indicators of determinant factors are also available.

DAIRY CALVES

Mortality Rates

Mortality rates of neonatal calves reported in the literature are often subdivided into **perinatal mortality,** which frequently—but not consistently—includes stillborn calves, and **postnatal mortality,** which in most cases includes calf mortalities occurring from 48 or 72 h onward to several months of age. Comparing numbers from different studies is difficult not only because of different definitions of the perinatal and postnatal periods, but also because some studies include all births, whereas others only include births of heifer calves.

Perinatal Mortality Rates

Perinatal mortality rates for dairy calves reported from countries with a developed dairy industry range from 2% to 10%, with a consistently increasing trend over the past decades.[4,5] The majority of perinatal deaths, approximately 75%, are considered to occur in the first hour of life, with the remainder occurring either before parturition (approximately 10%) or between 1 and 72 h after birth (approximately 15%).[4] Mortality rates in dairy calves in the first 24 h of life are between 6.5% and 9.7%.[6,7]

Neonatal Mortality Rates

Studies reporting neonatal mortality rates in calves, defined as mortality from day 3 of life on, are difficult to compare because different time ranges are considered, and some studies include all calves, whereas others only include heifer calves. In a recent U.S. study including 1138 births, a mortality rate of 4.6% for the period until 135 days of life was reported; a French study based on over 3 million calvings determined a mean mortality rate of 4.2% for the period between 3 and 30 days for the years 2005/2006.[8,9] In general, mortality rates for the perinatal period (0 to 48 h) tend to be higher than mortality rates for neonatal calves (from 3 days on), which underscores how critical the perinatal period is for the newborn calf.

Mortality rates for unweaned dairy heifers in the United States were surveyed repeatedly between 1996 and 2007 and were found to have declined from 10.8% in 1996 to 7.8% in 2007.[10]

Fetal Disease/Abortion

Abortion is a term generally used to describe the expulsion of a dead fetus from 45 to 265 days of gestation. A large dairy survey conducted in the United States in 2007 estimated that approximately 4.5% of all pregnant dairy heifers and cows had aborted in 2006.[13] The majority of these have no diagnosed cause.

Major Causes

Perinatal Mortality

The exact cause of death in the perinatal period, which often includes stillborn and weakborn calves, frequently remains undetermined. Epidemiologic studies investigating the risk factors for perinatal mortality in dairy calves have identified a number of genetic and nongenetic factors that are consistently associated with perinatal mortality.[4,7,11,12] Dystocia has consistently been identified as the single most important factor associated with perinatal mortality. Reported odds ratios (ORs) vary widely (2.7 to 14.6), but suggest that calves requiring assisted delivery have a 2.7 to 14.6 higher risk of death in the perinatal period than spontaneously born calves.[4] Other factors contributing to perinatal mortality include **lactation number** (calves born from heifers being more likely to die in the first hours of life than calves from multiparous cows), **birth weight** (calves with a birth weight of less than 20 kg and over 60 kg being at increased risk),[7] and **days of gestation** (calves born before 272 days of gestation being 6.7 times more likely to die than calves born between 272 and 302 days of gestation).[7] The OR for the death of a **twin calf** in the perinatal period was estimated at 13.4 times greater compared with singleton calves.[4]

Calving-associated anoxia may be an important contributing factor in these deaths.

Postnatal Mortality

Mortalities of neonatal dairy calves in the first days and weeks of life are attributable in large part to diarrheal disease. In a large survey conducted in the United States in 2007, diarrhea was by far the most common cause of death in unweaned dairy heifers, accounting for 56.5% of all deaths in that age category.[13] Other causes included respiratory problems (22.5%), undetermined causes (7.8%), lameness or injury (1.7%), and navel or joint infections (1.6%).[13]

Postnatal Disease

Calves are at highest risk for death in the first 2 weeks of life and especially in the first week. Septicemic and enteric diseases are most common during this period, with respiratory disease being more common after 2 weeks of age. **Failure of transfer of passive immunity** is a major determinant of this mortality.[14] The economic significance of neonatal disease can be considerable, and the occurrence of disease as a calf can also subsequently affect days-to-first-calving intervals and long-time survival in the herd. Death also causes a loss of genetic potential, both from the loss of the calf and the reluctance of the farmer to invest in higher-priced semen in the face of a calf mortality problem.

Meteorologic or **seasonal influences** may have an effect on dairy calf mortality rate,

and this can vary with the region.[4,7] In cold climates during the winter months, an increase in mortality may be associated with the effects of cold, wet, and windy weather, whereas in hot climates there may be an increase in mortality during the summer months in association with heat stress.

Management

Management is a major influence, and in well-managed dairy herds, calf mortality usually does not exceed 5% from birth to 30 days of age. Risk factors for disease morbidity and mortality in dairy calves relate to the **infection pressure** to the calf and factors that affect its **nonspecific** and **specific resistance** to disease. It is generally recognized that mortality is associated with the **type of housing** for calves, calving facilities, the person caring for the calves, and attendance at calving.[4] Thus calves that are born in separate calving pens have a lower risk of disease than those born in loose housing or stanchion areas, and the value of good colostrum feeding practices is apparent. Studies on the role of calf housing and the value of segregated rearing of calves in reducing infection pressure generally show beneficial health results.

The quality of management will be reflected in rates of failure of transfer of passive immunity and will also affect the infection pressure on the calf during the neonatal period. Quality of management is very hard to measure but is easily recognized by veterinary practitioners.

The epidemiologic observations that calf mortality is lower when females or family members of the ownership of the farm manage the calves, rather than when males or employees perform these duties, is probably a reflection of this variation in quality of management and suggests that owner managers and family members may be sufficiently motivated to provide the care necessary to ensure a high survival rate in calves. Even so, calf health can be excellent with some hired calf-rearers and very poor with some owner calf-rearers.

BEEF CALVES

Mortality Rates

Mortality in beef herds is usually recorded during the period from birth to weaning and has ranged from 3% to 7% in surveys, with higher rates in calves born to heifers; significantly higher mortality can occur in herds with disease problems. In a survey conducted in the United States in 2007, a perinatal mortality rate (including stillbirths) of 2.9% and a postnatal mortality rate (for the period from birth to weaning) of 3.5% was determined.[15] The majority of this mortality occurs within the first week of life, and most of it occurs in the parturient or immediate postnatal period as a result of prolonged birth or its consequences.

Major Causes

Dystocia resulting in death is common, and dystocial calves, twin-born calves, and calves born to heifers are at greater risk for postnatal disease. Enteric and respiratory diseases occur in outbreaks in some years, and very cold weather can result in high loss from hypothermia. In a 2007 survey conducted in the United States, beef calf mortality before weaning was found to be attributable to birth-related problems in 25.7%, to weather-related causes in 25.6%, to undetermined causes in 18.6%, to digestive tract problems (including diarrhea) in 14.0%, and to respiratory tract problems in 8.2% of all deaths.[15] Diarrhea and other infectious diseases become the most important cause of death in calves from their third day of life on.

Fetal Disease

Abortion rates appear to be lower than in dairy cattle, usually less than 1%. The majority of these are not diagnosed as to cause, but of those that are, infectious abortion is the most common diagnosis.

Parturient Disease

Accurate prospective and retrospective studies have shown that 50% to 60% of the parturient deaths in beef calves are associated with slow or difficult birth and that the mortality rate is much higher in calves born to heifers than from mature cows. **Dystocial birth** can lead to injury of the fetus and to hypoxemia and may not necessarily be associated with fetal malposition. **Birth size** is highly heritable within all breed types of cattle, and perinatal mortality will vary between herds depending on their use of bulls with high ease-of-calving ratings in the breeding of the heifer herd. Milk fever and overfatness at calving are other preventable causes of mortality. Selective intensive supervision of calving of the heifer herd can also result in a reduction of perinatal mortality.

Postnatal Disease

Scours and pneumonia are the next most important causes of mortality in beef calves, followed by exposure to extremely cold weather or being dropped at birth into deep snow or a gully.[15] The incidence of diarrhea is greatest in the first 2 weeks of life, and there is considerable variation in incidence between herds. However, explosive outbreaks of diarrhea or exposure chilling can be significant causes of mortality in certain years. The purchase of a calf for grafting, often from a market, is a significant risk for introduction of disease to a herd.

The **body-condition score** of the dam can influence calf mortality; dams with high condition scores have a higher risk for dystocial mortality, and those with low scores have a higher risk for infectious disease. Mortality from diarrhea is often higher in calves born to heifers, possibly because heifers are more closely congregated for calving supervision or because of a higher risk for failure of transfer of passive immunity in this age group. Congenital abnormalities can be an occasional cause of mortality in some herds.

PIGLETS

Mortality Rates

Preweaning mortality rates in commercial pig farms reported from different parts of the world range between 11% and 20%, with more than 30% of the mortality occurring in the first 24 hours and more than 50% in the first 4 days of life.[16-18] Mortality increases as the mean litter size increases and as the mean birth weight of the piglets decreases. In most herd environments, the minimal **viable weight** is approximately 1 kg. The mean number of piglets weaned is related to the size of the litter up to an original size of 14 and increases with parity of sows up to their fifth farrowing. Preweaning mortality is negatively correlated with herd size and farrowing crate utilization, and it is positively correlated with the number of farrowing crates per room. The use of farrowing crates was found to reduce neonatal mortality by 50% in some studies, mainly as a result of decreased frequency of crushing of piglets by the sow.

Major Causes

Surveys of neonatal mortality in piglets have repeatedly indicated that the most important causes of death in piglets from birth to weaning are noninfectious in origin.[16,17,19] The major causes are **starvation and crushing** (75% to 80%; although these may be secondary to, and the result of, hypothermia), congenital abnormalities (5%), and infectious disease (6%). The major congenital abnormalities are congenital splayleg, atresia ani, and cardiac abnormalities. Infectious diseases may be important on certain individual farms but do not account for a major cause of mortality.

Fetal Disease

Fetal disease rates in most herds are low unless there is an abortion storm or poor control of endemic infections such as parvovirus. In contrast to other species, the majority of abortions are diagnosed and are infectious.

Parturient Disease

Stillbirths account for 4% to 8% of all deaths of piglets born, and 70% to 90% are type II or intraparturient deaths, in which the piglet was alive at the beginning of parturition.[16] The viability of newborn piglets can be accurately evaluated immediately after birth by scoring skin color, respiration, heart rate, muscle tone, and ability to stand. Stillbirths are more commonly born in the later birth orders of large litters, and it is a relatively

common practice for sows to be routinely given oxytocin at the time of the birth of the first piglet to shorten parturition. Controlled trials have shown that although oxytocin administration at this time will result in a significant decrease in farrowing time and expulsion intervals, there is a significant increase in fetal distress, fetal anoxia, and intrapartum death and an increase in piglets born alive with ruptured umbilical cords and meconium staining.

Postnatal Disease

The large percentage of mortality caused by **crushing** and trampling likely includes piglets that were starved and weak and thus highly susceptible to being crushed. The estimated contribution of crushing and starvation to neonatal mortality varies from 19% to 58% of liveborn mortality.[16] The body-condition score of the sow at the time of farrowing, the nursing behavior of the sow, the sow's ability to expose the teats to all piglets, and the sucking behavior of the piglets also have a marked effect on survival.

Cold stress is also an important cause of loss, and the provision of a warm and comfortable environment for the newborn piglet in the first few days of life is critical.[17] The lower critical temperature of the single newborn piglet is 34°C (93°F). When the ambient temperature falls below 34°C (93°F), the piglet is subjected to cold stress and must mobilize glycogen reserves from the liver and muscles to maintain deep body temperature. The provision of heat lamps over the creep area and freedom from draughts are two major requirements.

Management

Minimizing the mortality rate of newborn piglets will depend on management techniques, which include the following:

- Proper selection of the breeding stock for teat numbers, milk production, and mothering ability
- The use of farrowing crates and creep escape areas to minimize crushing injuries
- Surveillance at farrowing time to minimize the number of piglets suffering from hypoxia and dying at birth or a few days later
- Batch farrowing, which allows for economical surveillance
- Fostering to equalize litter size
- Cross-fostering to equalize nonuniformity in birth weight within litters
- Improvement in the thermal comfort of the piglets
- Supplemental iron
- Artificial rearing with milk substitutes containing purified porcine gammaglobulin to prevent enteric infection

FOALS

Mortality Rates

Foals are usually well supervised and cared for as individual animals. Neonatal death is less frequent than in other species, but equivalent rates of morbidity and mortality occur on some farms. Infectious disease is important, along with structural and functional abnormalities that are undoubtedly better recognized and treated than in any of the other large animal species. In a large survey of thoroughbred mares in the United Kingdom, only 2% of newborn foals died, only 41% of twins survived, and 98% of singles survived. In contrast, a mortality rate of 22% between birth and 10 days was recorded in an extensively managed system. A recent retrospective study from Ireland determined a foal mortality rate of 5% during the first 12 months; 64.7% of deaths occurred during the first 30 days, and 82% of all deaths occurred within the first 6 months of life.[20]

Major Causes

Fetal Disease

Fetal disease is a major cause of loss; in one study, infections accounted for approximately 30% of abortions. In a retrospective study of 1252 fetuses and neonatal foals submitted for postmortem examination over a 10-year period in the United Kingdom, equine herpes virus and placentitis accounted for 6.5% and 9.8% of the diagnoses, respectively. The placentitis occurred in late gestation, was concentrated around the cervical pole and lower half of the allantochorion, and was associated with ascending chronic infections of bacteria or fungi resident in the lower genital tract.

Parturient Disease

Neonatal asphyxia, dystocia, umbilical cord abnormality, congenital abnormalities, and musculoskeletal trauma are important causes of foal mortality. A retrospective study from Ireland found that 45.5% of all deaths that occurred in the first 30 days of life were attributable to congenital abnormalities, 18.2% to the perinatal asphyxia syndrome, and 18.2% to musculoskeletal trauma.[20] In a UK study, umbilical cord disorders accounted for 38.8% of the final diagnoses. Umbilical cord torsion usually resulted in death of the fetus in utero, but the long cord/cervical pole ischemia disorder resulted in intrapartum death and a fresh fetus with lesions consistent with acute hypoxia.

Twins are at higher risk for spontaneous abortion.

Postnatal Disease

Postnatal disease causing mortality from birth to 2 months of age includes lack of maturity (36%), structural defect (23%), birth injury (5%), convulsive syndrome (5%), alimentary disorder (12%), generalized infection (11%), and other (miscellaneous; 9%). Of the **infectious diseases**, gastrointestinal and septicemic diseases have the greatest importance. Whereas in the past many of these conditions would have been fatal, significant advances in the science of equine perinatology were made in the 1980s and 1990s, and protocols for the treatment of neonatal disease have been developed that are based on equivalents in human medicine. These have proved of value in the management and treatment of prematurity, immaturity, dysmaturity, and neonatal maladjustment syndromes in newborn foals and in enteric and septicemic diseases. Different levels of intensive care have been defined, starting from those that can be applied at the level of the farm and increasing in sophistication, required facilities, and instrumentation to those that are the province of a specialized referral hospital. Early follow-up studies indicate that this approach is of considerable value in foals with neonatal disease and that most surviving foals become useful athletic adults.

NEW WORLD CAMELID CRIAS

Mortality Rates

Mortality of newborn llamas and alpacas is low compared with other production animal species, which in part because New World camelids (NWCs) are frequently kept as companion animals and receive better attention and more intensive treatment in cases of disease. Preweaning mortality rates for llama and alpaca crias are in the range of 2% to 6%, with the great majority of deaths occurring in the first week of life.[21,22]

Major Causes

Fetal Disease

Abortion and fetal loss after 100 days of gestation have been estimated to occur in 5% of all pregnancies in NWCs.[23] Common noninfectious causes for abortion include stress (e.g., related to transport), nutritional deficiencies, and iatrogenic administration of PGF2α or glucocorticoids. Documented infectious causes for abortion include toxoplasmosis, brucellosis, chlamydiosis, listeriosis, leptospirosis, and neosporosis.[23]

Parturient Disease

Perinatal mortality of crias is strongly associated with the course of parturition and the age of the dam at birth. Dystocia and assisted birth clearly increase the risk for postnatal morbidity and perinatal and postnatal mortality in NWC crias, as in other species.[21]

Postnatal Disease

The great majority of preweaning mortality occurs in the first week of life, and hypothermia and starvation were determined to be the most common causes of death. Low birth weight was found to considerably increase the risk of perinatal death, as was young age of the dam. Primiparous dams 2 to 3 years old give birth to lighter calves than do older dams and are considered to produce less

colostrum, and of inferior quality, than their multiparous herd mates. Small crias have more difficulties standing and getting sufficient amounts of colostrum and lose more body heat because of greater body surface relative to body mass, and thus they are at increased risk of starving to death or of developing perinatal or postnatal diseases.[21] A difficult parturition negatively affects perinatal vitality and thereby considerably increases the risk for postnatal morbidity and mortality.[22]

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PERINATAL DISEASE—SPECIAL INVESTIGATION OF ANY NEONATAL DEATHS (ILLNESS)

The following protocol is a generic guide to the investigation of deaths of newborn animals. It will require modification according to the species involved.

1. Determine the duration of pregnancy to ensure that the animals were born at term.
2. Collect epidemiologic information on the problem. Where possible, the information should include the following:
   - What is the abnormality?
   - What are the apparent age at onset and the age at death?
   - What clinical signs are consistently associated with the problem?
   - What is the prevalence and proportional risk in particular groups (maternal, paternal, nutritional, vaccinated, etc.)?
   - What is the parity of the dam that gave birth to the animal, and what proportional risk does this reflect within the group?
   - What is the birth history of affected animals? Are births supervised, and if so, what is the frequency of observation and what are the criteria for intervention? What is the proportional risk associated with prolonged birth?
   - Is there an effect of litter size, and what is the health of the other littermates?
   - Was there any difference in management of the dams of the affected animals compared with the group as a whole?
   - What is the farm policy for feeding colostrum?
   - What were the environmental conditions during the past 48 hours? (In housed animals, the quality of the environment should be measured objectively.)
3. Conduct a postmortem examination of all available dead neonates. The determination of body weight is essential, and measures of **crown–rump length** can also give an indication of gestational age. In order of precedence, the purpose of the postmortem examination is to determine:
   - The time of death in relation to parturition (e.g., fetal disease, parturient disease, early or delayed postnatal death). This can be determined from the state of the lungs, the nature of the severed end of the umbilical artery and the presence of a clot, the state of the brown-fat deposits, whether the animal has walked, and whether it has suckled before death.
   - The possibility that animals born alive have died because of cold stress, hypoglycemia, and starvation. An indication can be obtained from an examination of the brown-fat reserves and observation of the presence or absence of milk in the gastrointestinal tract and fat in the intestinal lymphatics. The presence of subcutaneous edema in the hind limbs is also relevant.
   - The possible presence of birth injury or trauma. In addition to examination of the ribs and liver for trauma and the presenting areas for subcutaneous edema, the brain should be examined for evidence of hemorrhage.
   - The presence of infectious disease. If necessary, samples can be submitted for examination.
   - The presence of congenital disease
4. If abortion is suspected, specimens of fetal tissues and the placenta are sent for laboratory examination. Examinations requested are pathologic and microbiological for known pathogens for the species of animal under consideration.
5. A serum sample should be collected from the dam for serologic evidence of teratogenic pathogens, followed by another sample 2 weeks later. Samples from unaffected dams should also be submitted. A precolostral serum sample from affected animals may assist in the diagnosis of intrauterine fetal infections.
6. Investigate management practices operating at the time, with special attention to clemency of weather, feed supply, maternalism of dam, and surveillance by the owner—all factors that could influence the survival rate. Where possible, this should be performed using objective measurements. For example, in calf-rearing establishments, the efficacy of transfer of colostral immunoglobulins should be established by the bleeding of a proportion of calves and actual measurement, food intake should be established by actual measurement, and so forth.

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Perinatal Disease—Congenital Defects

SYNOPSIS

Etiology Genetic, infectious, toxic, and physical causes are recognized for some defects, but the etiology of most is not known.

Continued

Epidemiology Low but significant incidence in all animals; epidemiology depends on cause.

Clinical findings Congenital defects can be structural or functional; clinical signs depend on organ system(s) affected.

Clinical pathology Specific serologic and biochemical tests can be used in the diagnosis and control of some congenital disease and, if available, are detailed under specific disease headings.

Necropsy findings Specific to the particular problem.

Diagnostic confirmation Abnormalities of structure or function that are present at birth are obviously congenital defects; they may or may not be inherited, and inherited defects may or may not be manifest at birth; genome analysis for inherited defects.

Control Avoidance of exposure to teratogenic agents; vaccination for some teratogenic infections; identification of carriers for genetic defects.

ETIOLOGY

Congenital disease can result from defective genetics or from an insult or agent associated with the fetal environment. A neonate with a congenital defect is an adapted survivor from a disruptive event of a genetic or environmental nature or of a genetic–environmental interaction at one or more of the stages in the sequences of embryonic and fetal development.

Genetic abnormalities may result in a wide spectrum of disorders that can vary from severe morphologic malformations to the presence of inborn errors of metabolism in animals that may be born apparently normal and develop disease later in life.

Susceptibility to injurious **environmental agents** depends on the nature and the severity (dose size and duration of application) of the insult and decreases with fetal age. Before attachment, the zygote is resistant to teratogens but susceptible to chromosomal aberrations and genetic mutations. Agents that disrupt blastula and gastrula stages and that interfere with normal apposition of the uterine mucosa are usually embryotoxic and induce early embryonic death.

The period during which an **organ system** is being established is a particularly critical period for that system, and different teratogens, if applied at that time, can produce similar defects. One example is the complex of arthrogryposis and cleft, which can occur in the calves of cattle grazing certain species of lupine, in calves infected in utero with Akabane virus, and as an inherited disease in Charolais calves.

Many noninherited congenital defects in animals occur in "**outbreaks**," which is a reflection of the exposure of the pregnant herd to a virus, poisonous plant, or other teratogen during a period of fetal susceptibility. Because this occurs in early pregnancy, it is often very difficult to determine the nature of this exposure at the time the animals are born.

Some teratogens are quite **specific** in the defect that they produce, and their action may be limited to a single species; a tentative diagnosis as to cause can be based on this association. Others produce a wide variety of abnormality that may also occur with other teratogens, and cause is less obvious.

The exact etiology of most congenital defects is unknown. Influences that are known to produce congenital defects are presented here.

Chromosomal Abnormality and Inheritance

Most chromosomal abnormalities are associated with poor fertility and early embryonic death. A few are structural or numerical aberrations of chromosomes. The importance of chromosomal abnormality to congenital defects in farm animals has not been studied extensively, but a study of 55 aborted and stillborn calves found 6 with an abnormal chromosome component. Chromosomal abnormality is usually associated with multiple deformations. Most chromosomal abnormalities are mutant genes, and the majority are inherited as recessive traits. There are many examples among domestic animals.

Viral and Other Infections

Members of the Bunyaviridae (Akabane virus, Cache valley virus, and Rift Valley fever virus), *Orbivirus* (bluetongue virus, epizootic hemorrhagic disease virus, and Chuzan virus), and *Pestivirus* (bovine virus diarrhea virus, border disease virus, and hog cholera virus) families; Japanese B encephalitis virus; and Wesselsbron virus are recognized teratogens. Other viruses also can result in fetal death without malformation. Examples are as follows:

- Akabane virus—this infection of pregnant cattle, sheep, and goats causes arthrogryposis, microencephaly, and hydrocephalus. Infection of, and disease of, the fetus depends on the stage of pregnancy and the fetus's immunologic status. In cattle infected between 76 and 104 days of pregnancy, hydranencephaly predominates; arthrogryposis predominates with infections between 104 and 173 days of gestation, and poliomyelitis predominates after 173 days. In sheep the window of susceptibility for congenital defects is between 30 and 50 days.
- Cache valley virus—congenital infection of lambs with Cache valley virus produces disease very similar to that produced by Akabane virus in cattle. The period of susceptibility for congenital defects is 36 to 45 days of pregnancy.
- Rift Valley fever virus infection of pregnant sheep results in placentitis and abortion, but attenuated vaccine strains produce arthrogryposis and brain defects.
- Bluetongue virus—vaccination of ewes with attenuated vaccine virus between days 35 and 45 of pregnancy causes a high prevalence of porencephaly in lambs. Natural infections of sheep (50 to 80 days of gestation) and cattle (60 to 120 days of gestation) can result in fetal death and resorption or the birth of stillborn animals, weakborn animals, and animals with hydrocephalus, hydranencephaly, and, occasionally, arthrogryposis. Similar defects are produced by Chuzan, Aino, and Kasba virus infections.
- Bovine viral diarrhea—infection with cytopathogenic strains before 100 days can result in abortion and mummification, cerebellar hypoplasia, and optic defects, including cataracts, retinal degeneration, and hypoplasia and neuritis of the optic nerves. Other defects are brachygnathia, curly coats, abortion, stillbirth, and mummification. Infection of the bovine fetus between 45 and 125 days of gestation with a noncytopathic biotype of the virus can result in the development of a persistently viremic and immunotolerant calf that is carried to term, is born alive, remains persistently viremic, and may later develop mucosal disease.
- Border disease virus—the window of susceptibility is from 16 to 90 days of gestation, and, depending on the fetal age at infection and the presence of a fetal immune response, fetal infection may result in fetal death, growth retardation, the birth of persistently infected lambs, or lambs born with hypomyelinogenesis, hydranencephaly, and cerebellar dysplasia. Coat defects may also be seen.
- Hog cholera virus—vaccination of sows with modified vaccine virus between days 15 and 25 of pregnancy produces piglets with edema, deformed noses, and abnormal kidneys. Natural infection with field virus can cause reproductive inefficiency and cerebellar hypoplasia in piglets.
- An unidentified virus is associated with the AII type of congenital tremor in pigs.
- Congenital infection with Wesselsbron virus and with Rift Valley fever is

recorded as producing central nervous system disease in cattle and sheep.
- Japanese B encephalitis virus in pigs can result in abortion or in the birth of weak, mummified, or stillborn piglets and live piglets with neurologic abnormalities. The window of susceptibility is from 40 to 60 days of gestation.
- Pseudorabies virus infection of the pregnant sow can result in myoclonia congenita in piglets.
- Viral, bacterial, and protozoal agents that produce abortion in animals can also produce intrauterine growth retardation and the birth of weakborn neonates that are highly susceptible to mortality in early life.

Nutritional Deficiency

Many congenital defects in animals are known to be caused by deficiencies of specific nutrients in the diet of the dam. Examples are as follows:
- Iodine—goiter and increased neonatal mortality are caused in all species; prolonged gestation occurs in horses and sheep. Congenital musculoskeletal lesions are seen in foals (congenital hypothyroid dysmaturity syndrome). Deficiency may result from a primary deficiency or be induced by nitrate or *Brassica* spp. Syndromes are also produced by iodine excess, often associated with feeding excess seaweed or seaweed products.
- Copper—enzootic ataxia in lambs can result from either to a primary copper deficiency or a secondary deficiency in which the availability of copper is interfered with by other minerals (e.g., molybdenum and iron).
- Manganese—chondrodystrophy and limb deformities in calves
- Vitamin D—neonatal rickets
- Vitamin A—eye defects, harelip, and other defects in piglets
- Vitamin E and/or selenium—congenital cardiomyopathy and muscular dystrophy
- Congenital cobalt deficiency is reported to reduce lamb vigor at birth and to increase perinatal mortality because of impaired immune function in the lamb. A similar effect on immune function in neonatal lambs and calves has been proposed with copper deficiency.
- Malnutrition of the dam can result in increased neonatal mortality and is suspected in the genesis of limb deformities and in congenital joint laxity and dwarfism in calves.
- Vitamin A deficiency induced by feeding potato tops or water with high nitrate content has been associated with congenital blindness in calves.

Poisonous Plants

The teratogenic effects of poisonous plants have been reviewed in detail. Some examples are as follows:
- *Veratrum californicum* fed to ewes at about the 14th day of pregnancy can cause congenital cyclopia and other defects of the cranium and brain in lambs, in addition to prolonged gestation. When fed at 27 to 32 days of pregnancy, it can produce limb abnormalities. Tracheal stenosis has been produced by feeding at 31 to 33 days of gestation. The alkaloid cyclopamine is the teratogenic substance.
- "Crooked-calf disease" is associated with the ingestion of *Lupinus* sp. during pregnancy. This is a major problem on some rangelands in western North America. There are approximately 100 species of *Lupinus* in Canada and the United States, but the disease has been mainly associated with *L. sericeus*, *L. leucophyllus*, *L. caudatus*, and *L. laxiflorus.* These species are thought to be toxic because of their content of anagyrine, but some piperidine alkaloids may also produce the disease. The disease has been reproduced by feeding anagyrine-containing lupines to pregnant cattle between 40 and 90 days of gestation, but it can occur with later feeding in natural grazing. The syndrome is one of arthrogryposis, torticollis, scoliosis, and cleft palate.
- *Astragalus* and *Oxytropis* spp. locoweeds cause limb contracture in calves and lambs, in addition to fetal death and abortion.
- Tobacco plants—ingestion of *Nicotiana tabacum* (burley tobacco) and *Nicotiana glauca* (tree tobacco) by sows between 18 and 68 days of gestation, with peak susceptibility between 43 and 55 days, can cause limb deformities in their piglets. The teratogen is the piperidine alkaloid anabasine. Cleft palate and arthrogryposis have also been produced experimentally in the fetuses of cattle and sheep fed *N. glauca* during pregnancy, but the plant is not palatable, and thus this is an unlikely cause of natural disease.
- *Conium maculatum*, poison hemlock, fed to cows during days 55 to 75 of pregnancy, to sheep in the period of 30 to 60 days of pregnancy, and to sows in the period of 30 to 62 days of pregnancy will cause arthrogryposis, scoliosis, torticollis, and cleft palate in the fetuses. Cattle are most susceptible. The piperidine alkaloids coniine and coniceine are responsible.
- *Leucaena leucocephala* (or mimosine, its toxic ingredient) causes forelimb polypodia (supernumerary feet) in piglets when fed experimentally to sows.
- Fungal toxicosis from the feeding of moldy cereal straw has been epidemiologically linked to outbreaks of congenital spinal stenosis and bone deformities associated with premature closure of growth plates in calves.

Farm Chemicals

Certain farm chemicals are associated with teratogenic effects, including the following:
- Some benzimidazoles (parbendazole, cambendazole, oxfendazole, albendazole netobimin) are important teratogens for sheep, producing skeletal, renal, and vascular abnormality when administered between 14 and 24 days of pregnancy.
- Methallibure, a drug used to control estrus in sows, causes deformities in the limbs and cranium of pigs when fed to sows in early pregnancy.
- Apholate, an insect chemosterilant, is suspected of causing congenital defects in sheep.
- The administration of trichlorfon to pregnant sows can result in the birth of piglets with cerebellar hypoplasia and congenital trembles.
- Organophosphates have been extensively tested and found to be usually nonteratogenic. A supposed teratogenic effect is probably more a reflection of the very common usage of these substances in agriculture (see the discussion in the section on poisoning by organophosphates).
- Griseofulvin given to a mare in the second month of pregnancy is suspected of causing microphthalmia and facial bone deformity in a foal.

Physical Insults

Physical insults can also result in fetal abnormalities; examples are as follows:
- Severe exposure to beta or gamma irradiation (e.g., after an atomic explosion) can cause a high incidence of gross malformations in developing fetuses.
- Rectal palpation of pregnancy using the amniotic slip method between 35 and 41 days of pregnancy in Holstein Friesian cattle is associated with atresia coli in the calf at birth, but there is also a genetic influence. It is probable that the cause is palpation-induced damage to the developing colonic vasculature.
- Hyperthermia applied to the dam experimentally causes congenital deformities, but this appears to have no naturally occurring equivalent. The most severe abnormalities occur after exposure during early pregnancy (18 to 25 days in ewes). Disturbances of central nervous system development are the most common. Defects of the spinal

cord manifest themselves as arthrogryposis. and exposure of ewes to high temperatures (42° C, 107.5° F) causes stunting of limbs; the lambs are not true miniatures because they have selective deformities, with the metacarpals selectively shortened. The defect occurs whether nutrition is normal or not. Hyperthermia between 30 and 80 days of pregnancy in ewes produces growth retardation in the fetus. Developmental abnormalities have been reproduced experimentally in explanted porcine embryos exposed to environmental temperatures similar to those that may be associated with reproductive failure resulting from high ambient temperatures in swine herds.

Environmental Influences

Currently, there is considerable interest in the possible teratogenic effects of human-caused changes in the environment. The concern is understandable because the fetus is a sensitive biological indicator of the presence of noxious influences in the environment. For example, after an accidental release of polybrominated biphenyls, much of the angry public commentary related to the probable occurrence of congenital defects. The noxious influences can be physical or chemical. In one examination of the epidemiology of congenital defects in pigs, it was apparent that any environmental causes were from the natural environment; human-caused environmental changes, especially husbandry practices, had little effect. A current concern in some regions is an apparent increase in congenital defects thought to be associated with exposure to radiofrequency electromagnetic fields associated with mobile telephone networks, but there are few hard data.

EPIDEMIOLOGY

Individual abnormalities differ widely in their spontaneous occurrence. The determination of the cause of congenital defects in a particular case very often defies all methods of examination. Epidemiologic considerations offer some of the best clues, but they are obviously of little advantage when the number of cases is limited. The possibility of inheritance playing a part is fairly easily examined if good breeding records are available. The chances of coming to a finite conclusion are much less probable. The determination of the currently known teratogens has mainly been arrived at following epidemiologic studies suggesting possible causality followed by experimental challenge and reproduction of the defect with the suspected teratogen.

An expression of the **prevalence** of congenital defects is of very little value unless it is related to the size of the population at risk, and almost no records include this vital data. Furthermore, most of the records available are retrospective and based on the number of cases presented at a laboratory or hospital.

Reported prevalence rates of 0.5% to 3.0% for calves and 2% for lambs are comparable with the human rate of 1% to 3%. A much higher rate for animals of 5% to 6% is also quoted. A study of over 3500 cases of abortion, stillbirth, and perinatal death in horses found congenital malformations in almost 10%. A very extensive literature on congenital defects in animals exists, and a bibliography is available.

Some breeds and families have extraordinarily high prevalence rates because of intensive inbreeding. The extensive use, by artificial insemination, of certain genetics can result in a significant increase in the occurrence and similar nature of congenital defects when the bulls are carriers of genetic disease. The use of bulls that were carriers for complex vertebral malformation syndrome, for example, resulted in an approximately threefold increase in the presence of arthrogryposis, ventricular septal defect, and vertebral malformations in Holstein Friesian calves submitted to diagnostic laboratories in the Netherlands between 1994 and 2000.

Checklists of recorded defects are included in the Further Reading section.

PATHOGENESIS

The pathogenesis of many of the congenital defects of large animals is poorly understood, but it is apparent that the disease produced by each teratogen is likely to have its own unique pathogenesis. Congenital defects in large animals include defects induced from structural malformations, from deformations, from the destruction of tissue by extraneous agents, and from enzyme deficiencies, or from a combination of these.

Structural Malformations and Deformations

Structural malformations result from a localized error in morphogenesis. The insult leading to the morphogenic error takes place during organogenesis and thus is an influence imposed in early gestation. **Deformations** occur where there is an alteration in the shape of a structure of the body that has previously undergone normal differentiation. Deforming influences apply later in the early gestational period, after organogenesis.

Deformation is the cause of arthrogryposis and cleft palate produced by the piperidine alkaloids from *Conium maculatum* and *Nicotiana* spp. and by anagyrine from *Lupinus* spp., which produce a chemically induced reduction in fetal movements. Ultrasound examination of the normal fetus shows that it has several periods of stretching and vigorous galloping during a 30-minute examination period. In contrast, the fetus that is under the influence of anagyrine has restricted movement and lies quietly, often in a twisted position. Restricted fetal limb movement results in arthrogrypotic fixation of the limbs, and pressure of the tongue on the hard palate when the neck is in a constant flexed position inhibits closure of the palate. In experimental studies there is a strong relation between the degree and duration of reduced fetal movement, as observed by ultrasound, and the subsequent severity of lesions at birth.

Restriction in the movement of the fetus, and deformation, can also result from teratogens that produce damage and malfunction in organ systems, such as the primary neuropathy that occurs in the autosomal-recessive syndrome in Charolais cattle and the acquired neuropathy in Akabane infection, both of which result in arthrogryposis through absence of neurogenic influence on muscle activity.

It has been suggested, with some good evidence, that the etiology and pathogenesis of congenital torticollis and head scoliosis in the equine fetus are related to an increased incidence of transverse presentation of the fetus. Flexural deformities of the limbs are also thought to be a result of errors in fetal positioning and limited uterine accommodation, which may be further complicated by maternal obesity. Abnormal placental shape may also be important in the genesis of skeletal deformations.

Viral Teratogenesis

Viral teratogenesis is related to the susceptibility of undifferentiated and differentiated cells to attachment, penetration, and virus replication; the pathogenicity of the virus (cytopathogenic versus noncytopathogenic strains of bovine viral diarrhea); the effects that the virus has on the cell; and the stage of maturation of immunologic function of the fetus at the time of infection. Viral infections can result in prenatal death, the birth of nonviable neonates with severe destructive lesions, or the birth of viable neonates with growth retardation or abnormal function (tremors, blindness). The gestational age at infection is a major influence. In sheep infected with border disease virus between 16 and 90 days of gestation, the occurrence of the syndromes of early embryonic death, abortion, and stillbirth and the birth of defective, small, and weak lambs are related to the fetal age at infection. Certain viruses cause selective destruction of tissue and of organ function late in the gestational period, and the abiotrophies are examples of selective enzyme deficiencies. The pathogenesis of the viral diseases is given under their specific headings in later chapters.

Inherited Congenital Defects

A number of **inherited congenital defects**, some of which are not clinically manifest until later in life, are associated with specific

enzyme deficiencies. Examples are maple syrup urine disease (MSUD), citrullinemia, factor XI deficiency in cattle, and the lysosomal storage diseases. Inherited lysosomal storage diseases occur when there is excessive accumulation of undigested substrate in cells. In mannosidosis, the disease occurs as a result of an accumulation of saccharides caused by a deficiency of either lysosomal α-mannosidase or β-mannosidase. In GM_1 gangliosidosis, disease is caused by a deficiency of β-galactosidase; in GM_2 gangliosidosis, the cause is a deficiency of hexosaminidase.

The age at development of clinical signs and their severity are dependent on the importance of the enzyme that is deficient, the biochemical function and cell type affected, and, in storage disease, the rate of substrate accumulation. Factor XI deficiency is manifest with bleeding tendencies, but the condition is not necessarily lethal. In contrast, calves with citrullinemia and MSUD develop neurologic signs and die shortly after birth, whereas the onset of clinical disease can be delayed for several months with α-mannosidosis.

CLINICAL AND NECROPSY FINDINGS

The intention is to give details of the clinical signs of all the congenital defects here, but some general comments are necessary. Approximately 50% of animals with congenital defects are **stillborn**. The defects are usually readily obvious clinically. Diseases of the nervous system and musculoskeletal system rate high in most published records, which may be related to the ease with which abnormalities of these systems can be observed. For example, in one survey of congenital defects in pigs, the percentage occurrence rates in the different body systems were as follows:

- Bones and joints, 23%
- Central nervous system, 17%
- Special sense organs, 12%
- Combined alimentary and respiratory tracts (mostly cleft palate and atresia ani), 27%
- Miscellaneous (mostly monsters), 9%
- Genitourinary and abdominal wall (hernias), each 5%
- Cardiovascular system, 3%

In a survey of congenital defects in calves, the percentage occurrence rates were as follows:

- Musculoskeletal system, 24%
- Respiratory and alimentary tracts, 13%
- Central nervous system, 22%
- Abdominal wall, 9%
- Urogenital, 4%
- Cardiovascular, 3%
- Skin, 2%
- Others, 4%
- (Anomalous-joined twins and hydrops amnii accounted for 20%.)

In a survey of foals, the approximate percentage occurrence rates were as follows:

- Musculoskeletal system, 50%
- Respiratory and alimentary tracts, 20%
- Urogenital, 9%
- Abdominal wall, 6%
- Cardiovascular, 5%
- Eye, 5%
- Central nervous system, 5%

Contracted foal syndrome and craniofacial abnormalities were the most common congenital defects in a study of stillbirth and perinatal death in horses.

Many animals with congenital defects have more than one anomaly. In pigs, for example, the average is two, and considerable care must be taken to avoid missing a second and third defect in the excitement of finding the first. In some instances, the combinations of defects are repeated often enough to become specific entities. Examples are microphthalmia and cleft palate, which often occur together in piglets, and microphthalmia and patent interventricular septum in calves.

There are a number of defects that cannot be readily distinguished at birth and others that disappear subsequently. It is probably wise not to be too dogmatic in predicting the outcome in a patient with only a suspicion of a congenital defect or one in which the defect appears to be causing no apparent harm. A specific instance is the newborn foal with a cardiac murmur.

Sporadic cases of congenital defects are usually impossible to define etiologically, but when the number of affected animals increases, it becomes necessary and possible to attempt to determine the cause.

CLINICAL PATHOLOGY

The use of clinical pathology as an aid to diagnosis depends on the disease that is suspected and its differential diagnosis. The approach varies markedly with different causes of congenital defects: **specific tests** and procedures are available for some of the viral teratogens, for congenital defects associated with nutritional deficiencies, and for some enzyme deficiencies and storage diseases, and the specific approach for known teratogens is covered in the individual diseases section.

When an unknown viral teratogen is suspected, precolostral blood samples should be collected from the affected neonates and also from normal contemporaries that are subsequently born in the group. Precolostral serum can be used for investigating the possible fetal exposure of the group to an agent, and the buffy coat or blood can be used for attempted virus isolation. IgG and IgM concentrations in precolostral serum may give an indication of fetal response to an infecting agent even if the agent is not known and there is no serologic titer to known teratogenic agents.

Enzyme-based tests have been used to virtually eradicate carriers of α-mannosidosis in cattle breeds in Australia and New Zealand, and DNA-based tests are used to detect and eliminate the carriers of such diseases as generalized glycogenosis in cattle.

DIFFERENTIAL DIAGNOSIS

- The diagnostic challenge with congenital defects is to recognize and identify the defect and to determine the cause.
- Syndromes of epidemic disease resulting from environmental teratogens are usually sufficiently distinct that they can be diagnosed on the basis of their epidemiology combined with their specific clinical, pathologic, and laboratory findings and on the availability of exposure.
- Congenital defects occurring sporadically in individual animals pose a greater problem. There is usually little difficulty in defining the condition clinically, but it may be impossible to determine the cause. With conditions where there is not an obvious clinical diagnosis, an accurate clinical definition may allow placement of the syndrome within a grouping of previously described defects and suggest possible further laboratory testing for further differentiation.

The examination for cause of an unknown congenital defect is usually not undertaken unless more than a few newborn animals in a herd or area are affected in a short period of time with similar abnormalities. A detailed epidemiologic investigation will be necessary, which will include the following:

- Pedigree analysis. Does the frequency of occurrence of the defect suggest an inherited disease, or is it characteristically nonhereditary?
- Nutritional history of dams of affected neonates and alterations in usual sources of feed
- Disease history of dams of affected neonates
- History of drugs used on dams
- Movement of dams during pregnancy to localities where contact with teratogens may have occurred
- Season of the year when insults may have occurred
- Introduction of animals to the herd

The major difficulty in determining the cause of nonhereditary congenital defects is the long interval of time between when the causative agent was operative and when the animals are presented, often 6 to 8 months. Detailed clinical and pathologic examination of affected animals offers the best opportunity in the initial approach to determine the etiology based on the presence of lesions that are known to be caused by certain teratogens.

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INTRAUTERINE GROWTH RETARDATION

Intrauterine growth retardation is a special form of congenital defect. It is a failure to grow properly, in contrast to a failure to gain body weight, and occurs when the developmental age is less than the chronologic (gestational) age. **Runt** is a common colloquial agricultural term. Normal fetal growth rate is determined by genetic and epigenetic factors, and cross-breeding experiments suggest that fetal size is regulated by the embryonic/fetal genotype and also is an effect of maternal genotype. Litter size has an effect on birth weight in all species, most likely through effects on the placental delivery of nutrients and removal of waste products relative to total fetal mass. A **genetic** association with intrauterine growth retardation has been shown in Japanese Black calves.

There is a strong positive association between placental mass and fetal size at birth in all species, and the majority of cases of growth retardation result from inadequate placentation, disturbance in utero of placental blood flow, or placental pathology.

ETIOLOGY

There are a number of different etiologies.

Heat stress to ewes in the final third of pregnancy will result in intrauterine growth retardation, but the condition is not as severe as when ewes are exposed in the second third of pregnancy, which is the period of placental growth. Hyperthermia results in a redistribution of blood away from the placental vascular bed and a decrease in cotyledon mass, with consequent reduction in birth weight. The degree of growth restriction is directly related to the degree of hyperthermia to which the ewe is exposed and her heat tolerance. The growth retardation affects fetal weight more than fetal length, and although there is some reduction in the growth of the brain, it is relatively less than that of the internal organs, resulting in an increased brain : liver weight ratio at birth.

Viral infections, such as border disease and bovine virus diarrhea in ruminants and parvovirus in pigs, produce growth-retarded neonates, as do bacterial and other infections that result in placentitis.

Inadequate placentation is the cause of runt piglets. Runts are smaller and thinner and have disproportionately larger, domed heads compared with normal pigs. A deficiency in specific **trace elements** is suspect in some field cases of growth retardation in ruminants, but there is no evidence for deficient trace-element nutrition in runt pigs.

Inadequate nutrition can result in growth retardation in utero. Growth retardation can be produced in fetal pigs, lambs, and calves by **maternal caloric undernutrition**. Nutritional restriction in ewes reduces the number of placental lactogen receptors that mediate amino acid transport in fetal liver and glycogen synthesis in fetal tissue, leading to depletion of fetal liver glycogen stores. This has been postulated as a possible cause of the fetal growth retardation that accompanies maternal caloric undernutrition; runt pigs have a reduced metabolic rate and lower skeletal muscle respiratory enzyme activity. This deficiency persists after birth; runt pigs have a lower core temperature and a lessened ability to increase their metabolic rate and heat production in response to cold.

Paradoxically, **overnourishing the adolescent ewe** will also result in placental growth restriction and in utero growth retardation. This effect is most evident in the second third of pregnancy. This syndrome is accompanied by the birth of lambs with a shorter gestational age, commonly reduced by 3 days. It is thought that the fetal hypoxia and hypoglycemia that accompany placental insufficiency might stimulate the maturation of the fetal hypothalamic–pituitary–adrenal axis, initiating early parturition. The growth of those lambs that survive initially lags behind that of normal lambs, but there is compensatory growth and no difference in weight at 6 months of age.

Measurements that can be used to determine the presence of growth retardation in a **dead fetus** include crown–rump (anal) length, brain weight, body weight, ratios of brain to body weight, long-bone weight, and appendicular ossification centers. Formulas are available to determine the degree of growth retardation.

In the **live animal** the presence of radiodense lines in long bones and the examination of closure of ossification centers can provide evidence for prior stressors in pregnancy that induce fetal growth retardation, such as malnutrition or infection of the dam, that may not be found by other examinations.

Intrauterine growth retardation is accompanied by an impaired cellular development of tissues, such as the small intestine and skeletal muscle, and disproportionately large reductions in the growth of some organs, such as the thymus, spleen, liver, kidney, ovary, and thyroid. There is an associated impairment of thermogenesis, immune function, and organ function at birth. In lambs there is impaired development of secondary wool follicles.

The **survival** of fetuses with growth retardation requires special nutritional care and the provision of adequate heat; this topic is discussed in the section on critical care for the newborn. In large piggeries that practice batch farrowing, the survival of runts can be significantly improved by the simple practice of fostering them together in one litter on one sow so that they do not have to compete with larger-birth-size and more vigorous pigs, by ensuring adequate colostrum intake and adequate environmental warmth, and by feeding using a stomach tube in the first few hours of life, if indicated.

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Physical and Environmental Causes of Perinatal Disease

Neonatal animals are newborns. The definition of a neonate is not precisely defined in terms of age of the animal and likely will vary from species to species dependent on the ability of the newborn to survive relatively independently and on the maturity or degree of postnatal development. Most farm mammals can be considered neonates until they are 2 weeks of age.[1]

The health of neonates is determined by factors that influence their growth and development in utero and their capacity to adapt to extrauterine life. Neonates affected by intrauterine conditions that impede their normal development (intrauterine growth retardation or premature birth) might not be prepared for the rapid and extensive physiologic changes needed to survive after birth. Furthermore, conditions experienced by the newborn can adversely affect its health and well-being; key among these factors are adequate nutrition, transfer of passive immunity from the dam, a thermoneutral environment or protection from the adverse effects of

excessive cold or heat, and protection from risk of injury.

PERINATOLOGY

Clinical care of the newborn animal in large animal veterinary medicine has traditionally started at the time of birth, but there is a growing recognition of the importance of antenatal and parturient events to the subsequent viability of the neonate.[2] This has been particularly recognized by equine clinicians and has led to the clinical concept of perinatology. One purpose of perinatology is to expand the care of the neonate into the antenatal and parturient period through the use of measurements that reflect fetal health or that can predict risk to fetal viability. Measures that can be used are still being developed and evaluated, but the following discussion includes those that have apparent value.

HEART RATE

Fetal heart rate recorded by electrocardiography (ECG) or by ultrasound can be used as a measure of fetal viability, for the detection of twins, and as a monitor for fetal distress during parturition.[3] The fetal heart rate of foals declines during gestation (Fig. 19-1) to approximately 60 to 80 beats/min near to term, and that of fetal calves is approximately 110 beats/min during the final 2 weeks of gestation.[4]

It has been suggested that a base heart rate of 80 to 92 beats/min with baseline variations of 7 to 15 beats/min and occasional accelerations above this is normal for the fetal heart rate of equids, and that bradycardia is evidence of abnormality. Continued monitoring traces may be needed to assess fetal distress.

Cardiac arrhythmia is common at the time of birth and for the first few minutes following and is thought to result from the transient physiologic hypoxemia that occurs during the birth process.

An alternative to fetal ECG monitoring is use of per rectum or percutaneous ultrasonography to detect carotid or peripheral pulse rates in foals and calves.[4,5]

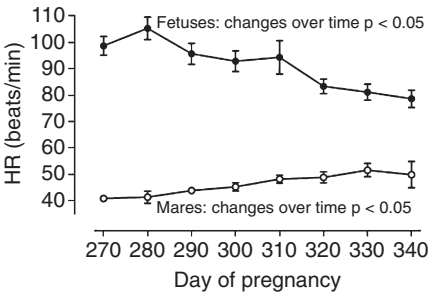

Fig. 19-1 Heart rate of mare and fetus from 270 days of gestation until foaling. The heart rate of the mare increases, whereas that of the foal declines, as the duration of gestation increases. (Reproduced from Nagel et al., 2011.[16])

ULTRASOUND EXAMINATION

The fetus can be examined by **ultrasound** to establish the presentation, the presence of twins, the heart rate, the presence and quality of fetal movement, the presence of placentitis, placental thickness, the presence of echogenic particles in the amniotic fluid, the depth of allantoic and amniotic fluid, and an estimate of body size from the measurement of the aortic and orbit diameters.[3,5-8] Measurements of fetal heart rate, fetal aortic diameter (an indicator of fetal size and, if measured near parturition, fetal birth weight),[8] uteroplacental contact, maximal fetal fluid depths, uteroplacental thickness, and fetal activity have allowed the development of objective measures to assess fetal well-being (Fig. 19-2).[6]

Clinicopathologic examination of samples of the **amniotic fluid** for the determination of pulmonary maturity and other measures of foal health is limited because there is a considerable risk for abortion and placentitis, even with ultrasound-guided amniocentesis, and the technique is not recommended for routine clinical use.

PREMATURITY

The average gestational length for mares is 343 days (range, 307 to 381), with the duration of gestation being longer for mares foaling later in the spring and for mares giving birth to a male foal (344 versus 341 days for a filly foal, respectively). There is no effect of breed of the mare or her age on gestational length.[9] Approximately 95% of mares were found to foal between 320 and 360 days of gestation, with 1.1% foaling at less than 320 days. Death rates were 8.3%, 3.6%, and 4.8% for foals born at less than 320 days, 320 to 360 days, and more than 360 days of gestation, respectively.[9] The difference was not statistically significant, but the number of foals born at less than 320 days was small (12), and this could have masked a statistical difference in case fatality rates. No foal lived if it was born at less than 311 days of gestation. Foals born at less than 320 days of gestational age are considered premature, and those born at less than 310 days are at significant risk for increased rate of death.[10]

Dystocia is associated with increased morbidity and case fatality rate in foals. Stage II labor lasting longer than 40 minutes is associated with increased risk of stillbirth (16×), death after birth (8×), and illness in the foal (2×).[9]

Similar data are available for cattle. For instance, in 41,116 calvings of Japanese Black cattle, there were 1013 stillbirths (2.46%) and 3514 dystocias (8.55%). Stillbirth rates were greater for those born at 301 or more days of pregnancy (OR: 1.049 [1.035 to 1.062]) and at 270 or fewer days of pregnancy (OR: 2.072 [2.044 to 2.101]) compared with those at between 281 and 290 days of pregnancy.[11] Among Holsteins, Jerseys, and crossbreds, gestation length was ~275 days, with male calves having a gestation length 1.2 days longer. The percentage of stillbirths was 6.6% across all observations, with 9.6% among first-parity dams and 5.1% among multiparous dams.[12]

Traditionally, external signs have been used to predict a premature foaling, and the common signs used are the enlargement of the udder, milk flow, and the occurrence of vaginal discharge. Causes of early foaling include bacterial or fungal placentitis and twin pregnancy. Several **assays** are used as alternate methods of determining whether foaling is imminent and if problems are present.

Plasma **progestogen** concentrations in mares decline in pregnancy to reach a low around 150 days of gestation. Plasma progestogen cannot be used to accurately predict the time of foaling, and a single sample is not diagnostic. There is a strong correlation between the presence of plasma progestogen concentrations above 10 ng/mL before a gestational age of 310 days and the presence of placental lesions, and a rapid drop in concentration to below 2 ng/mL that persists for more than 3 days indicates impending abortion. Current research is examining the profiles of individual progestogens during pregnancy to determine whether the profile of any progestogen can be used as a predictor of fetal distress.

There is considerable interest in predicting the time of parturition in mares. Recognition that significant changes occur in udder secretions during the last week of gestation, including a drop in pH on the day of foaling and increases in concentrations of calcium and potassium and declines in levels of sodium and chloride, has led to the development of several relatively simple tests.[13] These tests include measurement of the refractive index, pH, and calcium concentration of udder secretions during the week before anticipated parturition. Samples can be analyzed for calcium carbonate concentration using a water hardness kit, for pH with pH test paper, and for refractometry index with a Brix or similar refractometer. The positive predictive value (PPV) of parturition occurring within 72 hours and the negative predictive value (NPV) within 24 hours for calcium carbonate concentration (≥400 μg/g) were 94% and 98%, respectively.[14,15] The PPV within 72 hours and the NPV within 24 hours for the pH test (≤6.4) were 98% and 99%, respectively. The PPV within 72 hours and the NPV within 24 hours for the Brix test (≥20%) were 73% and 97%, respectively. The high negative predictive value of measurement of calcium concentrations (by either method) and pH provides a way of determining when the mare is not likely to foal within the next 24 hours.[14]

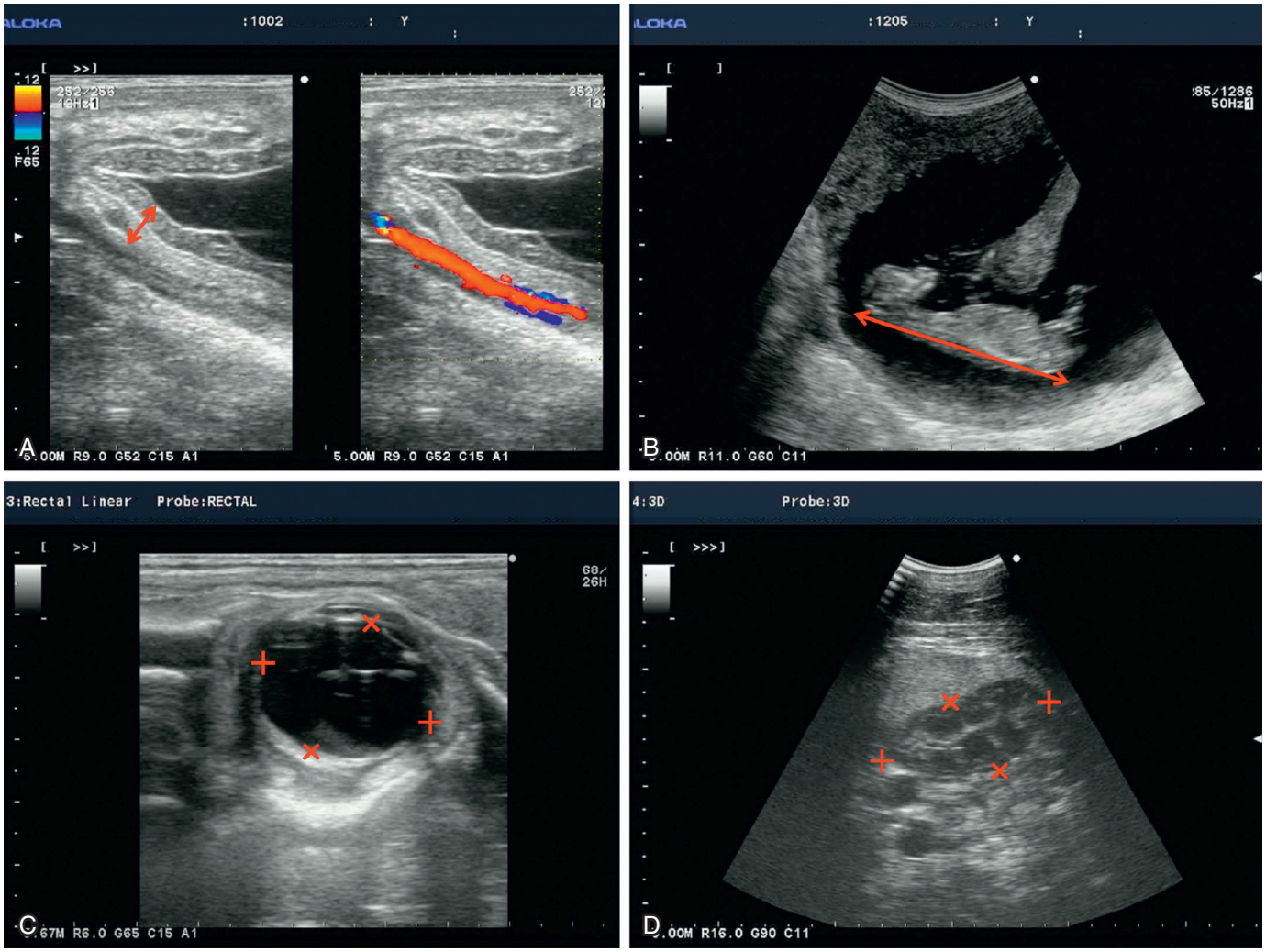

Fig. 19-2 Measurement of ultrasonographic indices of pregnant mare. **A,** Transrectal images in the ventral part of the uterine body, near the cervix. Headers show the combined thickness of the uterus and placenta (CTUP). **B,** Transrectal image of crown rump length (CRL) (header). **C,** Transrectal image of fetal eye orbit. Eye length (=) and width (×) measurements are shown. Eye length is measured from the maximum length of the inner margins of the vitreous body, and eye width is measured from the margin of the anterior portion of the capsule of the lens to the inner margin of the optic disc. **D,** Transabdominal image of the fetal abdomen at the level of the kidney. Kidney cross-sectional length (=) and width (×) measurements are shown. (Reproduced with permission from Murase et al., 2014.[6])

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PREMATURITY AND DYSMATURITY OF FOALS

Foals that are born before 300 days are unlikely to survive, and foals born between 300 and 320 days of gestation are considered premature but can survive (see earlier discussion).[1] **Premature foals** are characterized clinically by low birth weight, generalized muscle weakness, poor ability to stand, lax flexor tendons, weak or no suck reflex, lack of righting ability, respiratory distress, short and silky haircoat, pliant ears, soft lips, increased passive range of limb motion, and sloping pastern axis. Radiographs may show incomplete ossification of the carpal and tarsal bones and immaturity of the lung, and there may be clinical evidence of respiratory distress. **Full-term foals** born after 320 days of gestation but exhibiting signs of prematurity are described as **dysmature.**

Premature foals have hypoadrenal corticalism. They are neutropenic and lymphopenic at birth and have a narrow neutrophil-to-lymphocyte ratio. In premature foals older than 35 hours the neutrophil count can be used to predict survival, and foals that remain neutropenic after this time have a poor prognosis. Premature foals also have low plasma glucose, low plasma cortisol, and a blood pH of less than 7.25. An extensive collaborative investigation of equine prematurity has been conducted, and information on foal metabolism and guidelines for laboratory and clinical assessment

of maturity are available.[2] Foals that are born with clinical abnormalities suggestive of intrauterine growth retardation, prematurity, or dysmaturity are more likely to have an abnormal placenta and have higher serum concentrations of creatinine.[3]

The **placenta** is critical to the fetus in the antenatal period, and pregnancies involving placental lesions commonly result in foals that suffer premature-like signs at whatever stage they are delivered.[3,4] Placental edema, placental villous atrophy, and premature separation of the placenta are significant causes of fetal ill-health and delayed development.[5]

Precocious lactation of the mare can be associated with placentitis. The examination of the placenta for evidence of placentitis and for the presence of larger-than-normal avillous areas should be part of normal foaling management. There is a high correlation between both allantochorionic weight and area and foal weight in normal placentas. Normal placentas had a low association with subsequent perinatal disease in the foals.[3,4] In contrast, abnormal placental histology was associated with poor foal outcome (three normal foals from 32 abnormal placentas). Edema, sacculation, and strangulation are other abnormalities and can be associated with microscopic deposits of minerals within the lumen of placental blood vessels.

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PARTURIENT INJURY AND INTRAPARTUM DEATH

During parturition extreme mechanical forces are brought to bear upon the fetus, and these can result in direct traumatic damage or can impair fetal circulation of blood by entrapment of the umbilical cord between the fetus and the maternal pelvis, which can lead to hypoxemia or anoxia and death of the fetus during the birth process. Neonates that suffer birth trauma and anoxia but survive are at risk for development of signs of neurologic disease, have reduced vigor, are slower to suck, and are at increased risk for postnatal mortality.[1]

In all species, but in ruminants in particular, the **condition of the dam** can have a marked influence on the prevalence of birth injury and its consequences. The effect is well illustrated in sheep, where the two extremes of condition can cause problems. Ewes on a high plane of nutrition produce a large fetus and also deposit fat in the pelvic girdle, which constricts the birth canal, predisposing to dystocia. Conversely, thin ewes may be too weak to give birth rapidly. **Pelvic size** can influence the risk of birth injury, and ewe lambs and heifers mated before they reach 65% of mature weight are at risk. **Pelvimetry** is used to select heifers with adequate pelvic size for breeding, but the accuracy and validity of this method are seriously questioned. **Breed** is also a determinant of length and ease of labor and the subsequent quickness to time to first suckle.

TRAUMA AT PARTURITION

Traumatic injuries can occur in apparently normal births, with prolonged birth, and as a result of dystocia, which may or may not be assisted by the owner. Incompatibility in the sizes of the fetus and the dam's pelvis is the single most important cause of dystocia, and birth weight is the most important contributing factor. In cattle, expected progeny difference (EPD) estimates for calf birth weight are good predictors of calving ease. In foals, calves, and lambs the chest is most vulnerable to traumatic injury, but there is the chance of vertebral fracture and physical trauma to limbs with excessive external traction.[2]

Fractured ribs are common in foals and can lead to laceration of the lungs and heart and internal hemorrhage.[3] **Rupture of the liver** is common in some breeds of sheep and can also occur in calves and foals. A retrospective study of rib and vertebral fractures in calves suggests that most result from excessive traction and that, as a result, smaller dystocial calves are more at risk. **Vertebral fractures** occur as the result of traction in calves with posterior presentations and in calves with hip lock. Trauma is a major cause of neonatal mortality in piglets, but it occurs in the postparturient phase and is associated with being overlain or stepped on by the sow. It is possible that the underlying cause of crushing mortality in piglets is hypothermia.

Intracranial hemorrhage can result in damage to the brain. A high proportion (70%) of nonsurviving neonatal lambs at birth or within 7 days of birth have single or multiple intracranial hemorrhages, with the highest incidence being in lambs of high birth weight.[4] Similar lesions have been identified in foals and calves, but they are not a common finding in foals with neonatal maladjustment syndrome. Experimentally controlled parturition in ewes showed that duration and vigor of the birth process affected the severity of intracranial hemorrhages, and further studies indicated that these birth-injured lambs had depressed feeding activity and that they were particularly susceptible to death from hypothermia and starvation.

Birth anoxia associated with severe dystocia in cattle can result in calves with lower rectal temperatures in the perinatal period than normal calves and a decreased ability to withstand cold stress. Intracranial hemorrhage, especially subarachnoid hemorrhage, occurs in normal full-term deliveries as the result of physical or asphyxial trauma during or immediately following delivery.

In a prolonged birth, **edema** of parts of the body, such as the head and particularly the tongue, may also occur. Edema occurs particularly in the calf and the lamb, possibly because of less close supervision at parturition, and also because the young of these species can sustain a prolonged birthing process for longer periods than the foal without their own death or death of the dam. The edema can interfere with subsequent sucking, but the principal problem relative to neonatal disease is the effect of the often prolonged hypoxia to which the fetus is subjected. There is interference with the placental circulation and failure of the fetus to reach the external environment. The hypoxia may be sufficient to produce a stillborn neonate, or the neonate may be alive at birth but not survive because of irreparable brain damage. Intrapartum deaths resulting from prolonged parturition occur in piglets.

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FETAL HYPOXIA

Hypoxemia and hypoxia can occur as a result of influences during the birth process or because of pulmonary immaturity in premature births. The most common causes are dystocia, interrupted or restricted blood flow through the umbilical vein (carrying oxygenated blood to the fetus) and artery, and placental lesions, including premature separation of the placenta during labor, that reduce the effective surface area of the placenta in contact with the endometrium.[1] Intrapartum hypoxemia of the fetus resulting from **prolonged parturition** is common, particularly in calves born to first-calf beef heifers, and is presumed to be associated with the greater case fatality rate and morbidity in foals born after stage 2 labor of greater than 40 minutes.[2] Prolonged duration of parturition in ewes increases the risk of asphyxia (90× for each 10-min increase), decreases the viability score of lambs, and increases the latency to suckle the udder. Twin-born lambs were found to have a 16-fold greater risk of asphyxia.

Transient tachypnea occurs immediately after birth and is normal. **Prolonged tachypnea**, with flaring of the nostrils, open-mouth breathing, exaggerated rib retraction, and paradoxical breathing patterns, is highly suggestive of primary pulmonary abnormality. Failure of respiration can occur at this stage and creates an urgent need for resuscitation measures. In the foal, **body position** can have a major effect on arterial oxygen tension. A foal that is unable to stand or to right itself from lateral recumbency is at risk

from atelectasis and should be assisted to lie in sternal recumbency to stand. Hypoxia and hypercapnia resulting from mismatching of ventilation and perfusion are accentuated by prolonged recumbency.

Placental dysfunction or restriction of blood flow in the umbilical vessels during the second stage of labor can result in fetal hypoxia and death. Blood flow in umbilical vessels is reduced during uterine contractions and ceases during stage 2 labor in cattle as the calf's head appears at the vulva and just before delivery of the calf.[1] Before this stage, blood flow in the umbilical vein is significantly lower in acidotic than in nonacidotic calves, indicating impairment of oxygen delivery to the fetus and development of increased blood lactate concentrations.[1]

Fetal capillary blood pH and oxygen and carbon dioxide tensions can be measured during parturition, as is common practice in human obstetrics.[3] Fetal blood is collected from capillaries in the front feet as they project from the vulva by making a small incision (nick) in the skin and collecting blood into a capillary tube, which is then sealed before blood-gas analysis.[3] In 38 calves, some of which were born as a result of relieved dystocia or cesarean section, fetal capillary blood-gas values and pH (mean ± standard deviation [SD]) during the final 30 minutes of stage 2 labor were as follows: pH = 7.30 ± 0.10 (min 6.99, max 7.43), P_{O_2} = 19.5 ± 9.4 mm Hg, P_{CO_2} = 55.9 ± 26.0 mm Hg, HCO_3^- = 26.0 ± 4.4 mm Hg, base excess = −0.9 ± 5.3 mM/L, and oxygen saturation = 21.9 ± 16.6.[3] These compare with the following values in capillary blood obtained after recovery from birth in healthy calves: pH = 7.37 ± 0.11, P_{O_2} = 58.4 ± 17.0 mm Hg, P_{CO_2} = 38.1 ± 13.2 mm Hg, HCO_3^- = 20.8 ± 4.9 mm Hg, base excess = −3.2 ± 4.4 mM/L, and oxygen saturation = 82.4 ± 14.9%.[3] Similarly, jugular vein blood collected from 79 **lambs** immediately after birth (before onset of regular breathing) had the following values: pH = 7.21 ± 0.09 (range, 6.99 to 7.41), P_{O_2} = 18.4 ± 9.8 mm Hg (4 to 53), P_{CO_2} = 65.4 ± 12.5 mm Hg (29.6 to 103.7), HCO_3^- = 26.5 ± 4.0 mm Hg (13.9 to 35.4), base excess = −1.3 ± 5.1 mM/L (−16 to 9), and oxygen saturation = 21.2 ± 16.6% (0 to 85).[4] Both normal calves and lambs are acidotic, hypoxemic, and hypercapnic during birth as a result of impaired placental blood flow, and prolonged duration of stage 2 of parturition likely exacerbates this hypoxia and increases morbidity and fatality rate.[1]

A similar syndrome has been produced experimentally by clamping the umbilical cord of the bovine fetus in utero for 6 to 8 minutes, followed by a cesarean section 30 to 40 minutes later. Calves born following this procedure may die within 10 to 15 minutes after birth or survive for up to 2 days. During the experimental clamping of the umbilical cord, there is a decline in the blood pH, P_{O_2}, and standard bicarbonate levels and an increase in P_{CO_2} and lactate levels. There is also increased fetal movement during clamping and a release of meconium, which stains the calf and the amniotic fluid. Those that survive for a few hours or days are dull and depressed, cannot stand, and have poor sucking and swallowing reflexes, and their temperature is usually subnormal. They respond poorly to supportive therapy. A slight body tremor may be present, and occasionally tetany and opisthotonus occur before death. Calves that are barely able to stand cannot find the teats of the dam because of uncontrolled head movements. At necropsy of these experimental cases, there are petechial and ecchymotic hemorrhages on the myocardium and endocardium, there is an excess of pericardial fluid, and the lungs are inflated. When the experimental clamping lasts only 4 minutes, the calves usually survive.

Meconium staining (brown discoloration) of the coat of the newborn at birth is an important indicator that it has suffered hypoxia during or preceding the birth process,[5,6] and such neonates merit close supervision in the early postnatal period. In lambs, severe hypoxia during birth results in death within 6 days of birth. **Neurologic lesions** in lambs that died between birth and 6 days of age include hemorrhages in the meninges, brain congestion and edema, neuronal ischemic necrosis, intraparenchymal hemorrhages in the medulla oblongata and cervical spinal cord, parasagittal cerebral necrosis, and periventricular leukomalacia.[7] Edema was more severe in the brain than in other regions of the central nervous system. Ischemic neurons first appeared 24 hours postpartum, increased linearly in number between 48 hours and 5 days postpartum, and had a laminar distribution in the cerebral cortex, indicating a hypoxic-ischemic encephalopathy.[7] No significant lesions were found in anteparturient deaths or in those aged between 7 and 16 days. Lesions in the central nervous system can explain most deaths at birth and within 6 days of birth. The lesions were hypoxic-ischemic and appeared to be related to birth injury in some cases.[7] Similar lesions are not found in foals with neonatal maladjustment syndrome (see page 1871).

Fetal anoxia associated with **premature expulsion** of the **placenta** occurs in all species. Anoxia occurs in all parities of cow and with little relation to calving difficulty, although malpresentation is a predisposing factor. Prepartum diagnosis in cattle is hindered by the low prevalence of prepartum vaginal hemorrhage, and the majority of fetuses die during the birth process. The placenta is expelled with the fetus. **Premature separation** of the placenta ("red bag") occurs in foals and is an emergency that requires immediate attention. Premature placental separation occurs in approximately 1.6% of births and is associated with a case fatality rate of 18% in the foals.[2]

In all species the prevention of intrapartum hypoxia depends on the provision of surveillance. Universal surveillance is usually not practical for species other than the horse, and in cattle, for example, it tends to concentrate on the group at most risk so that surveillance, and assistance if necessary, is provided for first-calf heifers at the time of calving. Heifers that do not continue to show progress during the second stage of parturition should be examined for evidence of dystocia, and obstetric assistance should be provided if necessary.

The treatment and care of foals with this syndrome is described in the section on critical care of the newborn later in the chapter. The monitoring, treatment, and care of agricultural animals with this syndrome should follow the same principles but is usually limited by the value of the animal and the immediate access to a laboratory. Measures such as the time from birth to sternal recumbency, the time from birth to standing, and the time from birth to first suckle have been used to grade calves and identify those that might require intervention and treatment, but the best method of evaluation is an assessment of muscle tone. There is no effective practical treatment for calves affected with intrapartum hypoxia other than the provision of ventilation, as for the foal, and the correction of the acidosis. The airway should be cleared, and if physical stimulation of ventilation gives no response, then mechanical ventilation should be attempted. The practice of direct mouth-to-mouth ventilation assistance should be strongly discouraged, especially in lambs, because of the risk from zoonotic disease agents. Doxapram hydrochloride has been used in calves to stimulate respiration, but without demonstrated efficacy.

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HYPOTHERMIA IN NEWBORNS

The environment of the neonate has a profound effect on its survival. This is especially true for lambs and piglets, in which hypothermia and hypoglycemia are common causes of death. Hypothermia can also predispose to inadequate milk intake, including colostrum, and increase the risk and severity of infectious disease. A fuller description, including hypothermia affecting adults, is provided under "Hypothermia" in Chapter 5.

LAMBS

Cold stress and resultant death rates of lambs is an important animal welfare issue.[1] Lambs

are very susceptible to cold, and hypothermia is an important cause of mortality in the early postnatal period.[2] **Cold stress** to neonatal lambs is attributable to heat loss resulting from one or more of the factors of low ambient temperature, wind, and evaporative cooling. The healthy newborn lamb has a good ability to increase its metabolic rate in response to a cold stress by shivering and nonshivering thermogenesis (brown adipose tissue). The energy sources in the neonatal lamb are liver and muscle glycogen, brown adipose tissue, and, if it nurses, the energy obtained from colostrum and milk. The ingestion of colostrum can be essential for early thermogenesis in lambs, especially twin lambs.

The **critical temperature** (the ambient temperature below which a lamb must increase metabolic heat production to maintain body temperature) for light-birth-weight lambs is 31° C to 37° C (88°–99° F) in the first days of life.

The risk of death from hypothermia is highest in lambs of small birth size. **Heat production** is a function of body mass, whereas **heat loss** is a function of body surface area. Large-birth-size lambs have a greater body mass in relation to surface area and are thus more resistant to environmental cold stress. In contrast, small-birth-size lambs, with a smaller body mass relative to surface area, are more susceptible to chilling. The dramatic nature of this relationship was shown in early studies on cold stress and survival in lambs many years ago. Birth weight is lower in twins and triplets and in the progeny of maiden ewes. Susceptibility is also influenced by maternal nutrition in pregnancy (see the next section) because this can both influence placental mass, birth weight, and the energy reserves of the neonate and also affect the activity of the ewe at parturition, and the resultant poor mothering behavior and mismothering can result in starvation in the lamb.

Lambs are particularly susceptible to cold stress during the first 5 days of life. During this period hypothermia can result from heat loss in excess of summit metabolism or from depressed heat production caused by intrapartum hypoxia, immaturity, and starvation.

Heat loss is a function of the surface area available for convective, conductive, and evaporational heat loss; ambient temperature; wetness of the skin (fleece); and wind speed. These factors can be described mathematically as follows:

$$\begin{aligned} &\textit{Chill index}\ (kJ/m^2/hr) \\ &= 481 + (11.7 + 3.1 * V) * (40 - T) \\ &\quad - (418 * [1 - e^{-0.04Ra}]), \end{aligned}$$

where temperature (T), rain (Ra), and wind speed (V) are considered and are related to mortality rate in newborn lambs (Fig. 19-3).

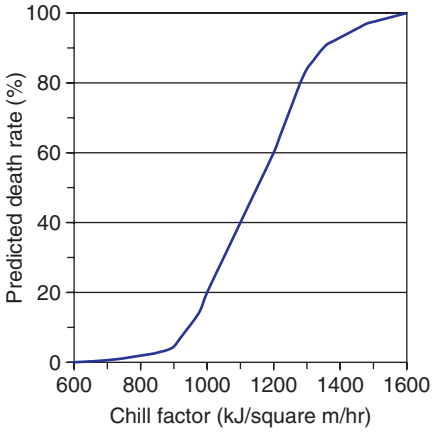

Fig. 19-3 Predicted death rate for neonatal lambs as a function of wind chill. (Data generated from LambAlive. Horizon Agriculture [www.hzn.com.au/lambalive.php] and courtesy of Dr. John Larsen, University of Melbourne.[6,7])

Heat Loss in Excess of Summit Metabolism

Low-birth-weight lambs born into a cool environment where there is wind are especially susceptible because of the evaporative cooling of fetal fluids on the fleece. For a small newborn lamb, the evaporative cooling effect of a breeze of 19 km/h (12 mph) at an ambient temperature of 13° C (55° F), common in lambing seasons in many countries, can be the equivalent of a cold stress equivalent to 25° C (77° F). The heat loss in these circumstances can exceed the lamb's ability to produce heat (summit metabolism), and progressive hypothermia and death result. Hypothermia as a result of heat loss in excess of summit metabolism can also occur when there is rain or just with cold and wind. Death occurs primarily in the first 12 hours of life.

Hypothermia From Depleted Energy Reserves

Hypothermia occurring in lambs after 12 hours of age is usually a result of depletion of energy reserves in periods of cold stress; milk is the sustaining energy source. There are three major causes of hypothermia from depleted energy reserves.

One of the early manifestations of developing hypothermia is the **loss of sucking drive**; severe cold stress and developing hypothermia can result in behavioral changes that cause low milk intake and subsequent depletion of energy reserves.

The second important cause is **mismothering**; the third is related to **birth injury**. Most researched measures of maternal behavior, temperament, and lambing difficulty are poorly correlated genetically with lamb survival.[3] Dystocia-related hypoxia is associated with acidemia, a reduction in summit metabolism, and disturbance in thermoregulation and can result in hypothermia. Birth-injured lambs, usually large single-born lambs, have depressed sucking and feeding activity, and actions to increase the birth weight of lambs above a certain point are likely to be counterproductive.[4] The relationship between mortality of lambs and birth weight is a U-shaped curve, with smaller and larger lambs at increased risk of death.[2]

In lambs that have hypothermia associated with heat loss in excess of summit metabolism, heat is required for **therapy**, but in lambs with starvation hypothermia the administration of glucose is also necessary. Glucose is administered intraperitoneally at a dose of 2 g/kg body weight using a 20% solution. Following the administration of the glucose, the lambs should be dried with a towel if wet and rewarmed in air at 40° C (104° F). This can be done in a warming box using a radiant heater as the heat supply. Care should be taken to avoid hyperthermia. Careful attention must be given to the nutrition of the lambs after rewarming; otherwise, relapse of hypothermia will occur. A feeding of 100 to 200 mL of colostrum will also be beneficial, but lambs should not be fed before they are normothermic because aspiration pneumonia is a risk. Experimental hypothermia in lambs has shown little direct long-term pathologic effect.

In most countries the selection of time of lambing is dictated by nutritional considerations and the seasonality of the ewes' sexual behavior, and lambing occurs at a time of year when cold stress is likely. The **control** of loss from hypothermia in newborn lambs requires supervision at lambing and protection from cold. Shed lambing will reduce cold-stress loss. The provision of shelter in lambing paddocks is effective at reducing mortality rate and in increasing profitability.[5] The site is important because birth sites in lambing paddocks are not randomly distributed, and there is variation in the preferred sites between breeds. Some ewes will seek shelter at lambing, but many ewes in wool will not. In some flocks, sheep are shorn before lambing in an attempt to force this shelter-seeking trait.

Experimentally, there is a strong relationship between breed and the degree of hypothermia produced. There is also convincing evidence that rearing ability is heritable in sheep, that some of this relates to traits within the newborn lamb, and that a significant reduction in neonatal mortality associated with susceptibility to hypothermia could be achieved with a genetic approach.

Lambs are also susceptible to **hyperthermia,** and thermoregulation is not efficient at high environmental temperatures. Heat prostration and some deaths can occur in range lambs when the environmental temperature is high, especially if lambs have to perform prolonged physical exercise and if there is an absence of shade.

CALVES

Hypothermia as a result of environmental influence is less common in full-term healthy calves than in lambs, but mortality rates have been shown to increase with decreasing ambient temperature and increasing precipitation on the day of birth. The **critical temperature** for neonatal calves is much lower than that for lambs, approximately 13°C (55°F), and *Bos taurus* calves are more resistant to cold stress than are *Bos indicus.*

Experimentally produced hypothermia in calves causes little overt injury except for peripheral damage to exterior tissues. During cooling there can be significant peripheral hypothermia before any marked reduction in core body temperature. Calves have a remarkable ability to resist and overcome the effects of severe cold temperatures. However, there is a relationship between the occurrence of cold weather and calf deaths, including those resulting from "weak-calf syndrome," and deficiencies in thermoregulation occur in animals born prematurely and in dystocial calves. As in lambs, dystocia will reduce teat-seeking activity and sucking drive, and dystocial calves have lower intakes of colostrum, lower body temperatures, and decreased ability to withstand cold stress.

Rewarming of hypothermic calves can be by radiant heat, but immersion in warm water produces a more rapid response and with minimal metabolic effort. The prevention of hypothermia requires the provision of shelter from wet and wind for the first few days of life. Cows can be calved in a shed; alternatively, sheds for calves can be provided in the fields. Beef calves will use shelters in inclement weather; these may not improve their health status, although they are in common use.

PIGLETS

Hypothermia from heat loss and hypothermia/hypoglycemia from starvation are major causes of loss in neonatal pigs. Newborn piglets have a reasonably good ability to increase their metabolic rate in response to cold stress, but they have limited energy reserves, especially limited brown adipose tissue, and they consequently rely on a continual intake of milk for their major energy source, sucking approximately every hour. Young pigs have a good ability for peripheral vasoconstriction at birth, but surface insulation is deficient because at this age there is no subcutaneous layer of fat. The **critical temperature** for young pigs is 34°C (93°F).

Thermoregulation is inefficient during the first 9 days of life and is not fully functional until the 20th day. Newborn piglets must be provided with an external heat source in the first few weeks of life. The body temperature of the sow cannot be relied upon for this, and the preferred air temperature for neonatal pigs is 32°C (89.5°F) during the first day and 30°C (86°F) for the first week. In contrast, the preferred temperature for the sow is about 18°C (64°F). A **separate environment** (creep area) must be provided for the piglets. Provided that there is an adequate ambient temperature to meet the requirements of the piglets and good floor insulation, hypothermia will not occur in healthy piglets of viable size unless there is a failure of milk intake.

Birth anoxia, with resultant reduced vigor, reduced teat-seeking activity, and **risk for hypothermia**, occurs particularly in later-birth-order pigs in large litters from older sows. Failure of milk intake can also occur with small-birth-size piglets and is influenced by litter size, low number of functional teats relative to litter size, and teat-sucking order.

FOALS

There have been few studies on thermoregulation in foals, but the large body mass in relation to surface area renders healthy newborn foals, like healthy calves, relatively resistant to cold. Also, foals are less likely to be born in a hostile environment than are other farm animals. Significant foal mortality from hypothermia as a result of starvation and exposure can occur in extensively managed herds, and dystocia, low birth weight, and poor mothering are contributing factors.

Sick and **premature foals** can have difficulty in maintaining body temperature in normal environments, and the metabolic rates of sick foals and premature foals are approximately 25% lower than those of healthy foals.

The relatively larger ratio of surface area to mass, lower energy reserves, and lower insulation of the coat of premature foals, coupled with the lower metabolic rate, place them at particular risk for hypothermia. **Dystocial foals** also have lower metabolic rates, but dysmature foals appear to thermoregulate normally. Methods of investigation that allow postmortem differentiation of placental insufficiency, acute intrapartum hypoxemia, inadequate thermogenesis, and starvation as causes of mortality in foals are available.

Hypothermia should be suspected in premature foals when the rectal temperature falls below 37.2°C (99°F) and should be corrected with external warmth, rugging, or moving to a heated environment. If fluids are being administered, they should be heated to normal body temperature.

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MATERNAL NUTRITION AND THE NEWBORN

There is increasing evidence that the maternal environment for a fetus affects lifelong characteristics of offspring and the subsequent generation of offspring ("grandchildren"). Although the effects of the maternal environment on the development of offspring are complex and involve factors such as maternal nutrition and health during gestation, birth weight of the fetus, sex of the fetus, quality of lactation by the dam, and environmental conditions, there is now solid evidence of epigenetic effects ("programming") in determining the growth and productivity of offspring in domestic species, and reviews are available.[1-4] It is now well understood that factors such as maternal nutrition can have long-lasting effects on an animal's health and productivity and that these effects can be transmitted to progeny separate from changes in the genotype (DNA composition).[2] This phenomenon, recognized in human medicine,[5] is well documented in pigs and cattle[6,7] and has risen to have considerable economic importance as part of the Australian Lifetime Wool project.[8-10] The concept is that early life (including in utero) environmental conditions cause epigenetic changes that can persist for the life of the individual and that can be transmitted to offspring.

Epigenetic changes involve methylation of cytosine in cytosine-guanine dinucleotides and alteration of histones in genetic material such that the accessibility of DNA for transcription is reduced or eliminated. The result is that methylated genes are silenced and not transcribed. Methylation of DNA and histones thereby affects the phenotype of the animal because the changes are transmitted during mitosis to daughter cells. Epigenetic effects can be cell and organ specific and can be transmitted to offspring.

An associated phenomenon important to animal breeding is the concept of imprinted genes. Genomic imprinting is a phenomenon in mammals in which the father and mother contribute different epigenetic patterns to the fetus. A limited number of monoallelic expressed genes exert their effect in a parent-of-origin-specific manner through specific genomic loci in the parents' germ cells. For these genes, expression is restricted to one of the two parentally inherited chromosomes. Imprinted chromosomes are silenced, allowing the other chromosome to be expressed, which is referred to as maternally expressed/paternally imprinted or paternally expressed/maternally imprinted.[1] Although the number of genes that can imprint is limited, many of these genes encode for proteins that regulate a wide variety of biological processes, including embryonic and neonatal growth,

metabolism, and behavior.[1] Understanding of this process has followed observations on abnormalities in animals born as a result of assisted reproductive technologies (including in vitro fertilization and somatic-cell nuclear transfer cloning) that alter methylation of chromosomes in gametes.[1,11] (See "Disorders of Cloned Offspring," page 1870).

Fetal programming describes the lifelong effects of in utero exposure of the fetus to various conditions.[2] Experimental maternal undernutrition during gestation adversely affects intermediate energy metabolism in lambs tested at ~20 weeks of age, evident as lower insulin secretory capacity and greater tissue insulin sensitivity.[12] Some of the effects of in utero exposure to the fetus could have lifelong effects on attributes important for agricultural productivity. This has been demonstrated for sheep in the Lifetime Wool project, in which numerous studies have revealed the importance of providing optimal nutrition and body condition for ewes for both the ewes' productivity and the lifetime productivity of their lambs.[13,14] The body weight profile of Merino ewes determines the fleece weight and fiber diameter of their progeny, with an optimal weight profile of the ewe resulting in higher fleece weight and finer wool in the progeny.[8] It does not appear that nutrition of the ewe affects milk production by her daughter and, therefore, live weight at weaning of the ewe's daughter's progeny.[15]

There is interest in fetal programming and epigenetics for horses, but currently there are no practical implications, although these can be anticipated.[3,4]

Effects on both the dam and the fetus can occur from overfeeding or underfeeding of the dam,[9] and there can be effects from the influences of trace-element deficiencies or toxic substances. Severe **undernutrition** of the dam can affect fetal size and its thermogenic rate, with consequences as described earlier. Prepartum protein restriction has the greatest effect. Severe undernutrition of the dam can also lead to weak labor and increased rates of dystocia and can limit the development of the udder. Colostrogenesis may be impaired, with a greater risk of infectious disease in the neonate, and milk production may be significantly reduced or delayed, with a risk of starvation.

Most information is available for the effects of nutrition of the pregnant ewe on fetal growth rate, udder development, the availability of energy in the body reserves of fetuses at term, and the amount and energy content of colostrum. In sheep, maternal nutrition can have a significant influence on fetal growth rate and placental size.[16] The underfeeding of hill sheep in late pregnancy markedly reduces the term weight of the udder and the prenatal accumulation and subsequent rates of secretion of colostrum. A low plane of nutrition in late pregnancy results in a marked decrease in fetal body-lipid and brown-fat reserves, a marked reduction in the total production of colostrum, and a reduction in the protein concentration in colostrum during the first 18 hours after parturition. However, exposure of late pregnant ewes to cold by shearing increases lamb birth weight and lamb brown-fat reserves.

Inadequate nutrition can also result in in utero growth retardation. Growth retardation can be produced in fetal pigs, lambs, and calves by **maternal caloric undernutrition**. Nutritional restriction in ewes reduces the number of placental lactogen receptors that mediate amino acid transport in fetal liver and glycogen synthesis in fetal tissue, leading to depletion of fetal liver glycogen stores. This has been postulated as a possible cause of the fetal growth retardation that accompanies maternal caloric undernutrition. Runt pigs have a reduced metabolic rate and lower skeletal muscle respiratory enzyme activity. This deficiency persists after birth; runt pigs have a lower core temperature and a lessened ability to increase their metabolic rate and heat production in response to cold. Paradoxically, **overnourishing the adolescent ewe** will also result in placental growth restriction and in utero growth retardation. This effect is most evident in the second third of pregnancy. This syndrome is accompanied by the birth of lambs with a shorter gestational age, commonly reduced by 3 days. It is thought that the fetal hypoxia and hypoglycemia that accompany placental insufficiency might stimulate the maturation of the fetal hypothalamic–pituitary–adrenal axis, initiating early parturition.

Maximum lamb survival is achieved at intermediate lamb birth weights, and the **nutritional management** of the pregnant ewe in fecund flocks is very important. Ewes with multiple lambs can be selected using ultrasound and fed separately from those with singles. Pregnant maiden ewes should also be fed to their separate requirements. The recommendation is for a body-condition score of 3.0 to 3.5 at mating, with a fall of 0.5 in score during the second and third months of pregnancy and a subsequent rise in score to 3.55 to the point of lambing, and with a distinct weight gain in late pregnancy. Equivalent condition scores are also appropriate for other species.

Toxic substances and trace-element deficiencies can result in increased risk for fetal and neonatal mortality and are discussed under those headings. Of particular significance is the agalactia, prolonged gestation, and fetal distress at birth seen in mares fed grain contaminated with ergot (*Claviceps purpurea*) and in mares grazing tall fescue (*Festuca arundinacea*) containing the endophyte fungus *Acremonium coenophialum*.

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POOR MOTHER–YOUNG RELATIONSHIP

Any examination of neonatal mortality suspected of being caused by hypothermia, starvation, or infection as a result of failure of transfer of passive immunity, and even trauma by crushing in piglets, must take into account the possibility that poor mothering and a poor mother–young bond could be the primary cause. Inadequate maternal care leads to rapid death of the newborn under extensive conditions where there is no human intervention to correct the problem.[1] The defect is most likely to be on the side of the dam, but it may originate with the offspring, especially in those that are hypothermic.[2] A poor relationship may be genetic or nutritional, and, on the part of the offspring, it may be the result of birth trauma.

For both the dam and the young, there is a much greater chance of establishing a good bond if the animal has been reared in a group rather than as an individual. Because sight, smell, taste, and hearing are all important in the establishment of seeking and posturing to suckle activity by the dam and seeking, nuzzling, and sucking activity by the offspring, any husbandry factor that interferes with the use of these senses predisposes to mortality. Weakness of the offspring as a result of poor nutrition of the dam, harassment at parturition by overzealous attendants, and high growth of pasture are obvious examples. Poor mother–young relationship can be a problem in cattle, pigs, and sheep, and occasionally in horses, especially with extensive foaling practices. In pigs a poor mother–young relationship may be developed to an intense degree in the form of farrowing hysteria, which is dealt with under that heading. In sheep a poor mother–young relationship can be a significant contributor to neonatal death from starvation, especially

Table 19-1 Scoring system for assessing vigorousness of newborn lambs[2]

Score	Description
1	Does not stand for at least 40 min; little or no teat-seeking drive; does not appear alert or active
2	Attempts to stand after 30 min; low teat-seeking drive and tendency to follow ewe; shows some alertness but not very active; does not appear coordinated in attempts
3	Shakes head within 30 s; attempts to stand within 15 min; seeking teat within 10 min of standing; follows ewe but distracted by other moving objects; generally alert and active; coordination may be lacking
4	Attempts to stand within 10 min of birth; seeking teat within 5 min of standing; strong tendency to follow ewe; alert and active and well-coordinated movements
5	Attempts to stand within 5 min of birth; follows ewe closely; very alert and active

Table 19-2 Definitions for lamb behaviors[2]

Behavior	Definition
Shakes head	Lamb raises and shakes head
To knees	Lamb rolls onto chest, gathers legs under it, and pushes front half of the body up off the ground
Attempts to stand	Lamb supports bodyweight on at least one foot
Stands	Lamb stands unsupported on all four feet for > 5 s
Reaches udder	Lamb approaches ewe and nudges her in the udder region
Unsuccessful suck	Lamb places head under ewe in contact with the udder, but either fails to grasp the teat or releases it without sucking
Sucks	Lamb hold teat in its mouth and appears to be sucking with appropriate mouth and head movements, may be tail-wagging, remains in this position for > 5 s

in highly strung breeds such as the Merino, which have a higher mismothering rate than do Romney ewes.[2,3]

Bonding occurs rapidly after birth, although there is some minor variation between species, with bonding starting within a few minutes of birth in sheep but taking up to 2 to 3 hours in some horses, for example. The strength of bonding also appears to vary between species. The bonding of the dam to the neonate is usually quite specific, although this can be modulated by management systems, and the neonate may be less selective and will often attempt to suck other dams. With sheep lambed under intensive lambing practices, this can lead to high rates of mismothering and subsequent abandonment, when preparturient "robber" ewes adopt lambs from multiple births. A high degree of shepherding is required to minimize loss in these management systems, whereas in extensive systems a strong bonding is established if the ewe and lamb are allowed to remain relatively undisturbed on the lambing site for 6 hours. A scoring system is available to allow objective assessment of the vigor of newborn lambs (Tables 19-1 and 19-2).

There is evidence of genetic and parental (sire) effects on the ability of lambs to follow the dam and to avoid mismothering. These effects appear to be modest. [2,4,5]

Vaginal cervical stimulation and the central release of oxytocin are thought to be important in initiating maternal behavior, although caudal epidural anesthesia for delivery does not effect mothering or bonding. Sucking is also a major determinant. Recognition is olfactory and auditory and mediated by the release of neurotransmitters.

Bonding is often slower with primiparous dams and is also delayed where there is postpartum pain. A failure of bonding leads to rejection and abandonment of the neonate.

Maternal care is also important to neonatal survival, and there is significant difference in litter mortality from crushing and injury among sows related to sow behavior and their response to piglet distress calls. A description of normal and abnormal behavioral patterns of the mare and foal is available, and techniques for fostering have been described.

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TEETH CLIPPING OF PIGLETS

It is necessary to shorten the needle teeth of the upper and lower jaw of the newborn pig using a clean pair of sharp nail clippers or a grinding wheel. It is essential to practice good hygiene or infection of tooth roots can occur, leading to local inflammation and infection with the possibility of abscessation associated with *Fusobacterium* and *Trueperella*. It is not done before 6 hours of age because it will interfere with the absorption of colostrum. It is done to prevent damage to the sow's teats or to other piglets before 7 days after birth. Damage to the sow's teats will cause pain and reluctance to allow suckling. Damage to other piglets may interfere with the establishment of the "pecking order" in the litter.

Failure of Transfer of Passive Immunity (Failure of Transfer of Colostral Immunoglobulin)

The acquisition and absorption of adequate amounts of colostral immunoglobulins is essential to the health of ruminant, porcine, and equine neonates because they are born virtually devoid of circulating immunoglobulin. **Failure of passive transfer** (FPT) has been a commonly used term to describe the transfer of passive immunity (immunoglobulins, specifically IgG1 in colostrum) from the dam to the neonate. The process by which colostral immunoglobulin is absorbed is far from passive; it is an active and focused activity. Accordingly, FPT provides an incorrect summary of this process, and **failure of transfer of passive immunity** (**FTPI**) provides a more accurate descriptive term. Adequate antibody transfer is the cornerstone of all neonatal preventive health programs, but FTPI remains an important problem particularly affecting the dairy industry. Educational campaigns targeting dairy producers have been launched in the past decades, and, encouragingly, the prevalence of FTPI in dairy heifers in the United States decreased from over 40% in 1992 to 19% in 2007.[1]

Much of the description that follows refers to the calf because more studies on transfer of passive immunity have been conducted in calves. However, most of the information is applicable to the other species; where there are differences, these are mentioned.

NORMAL TRANSFER OF IMMUNOGLOBULINS

Immunoglobulins in colostrum are present in different concentrations. The major immunoglobulin in colostrum is IgG. IgG consists of two fractions, IgG_1 and IgG_2, which contribute 80% and 5% to 10%,

respectively, to the total colostral immunoglobulin concentration. IgM and IgA each account for approximately 5% of the colostral immunoglobulin content. IgG is concentrated in colostrum by an **active, selective, receptor-mediated transfer** from the blood of the dam across the mammary secretory epithelium. This transfer to colostrum begins approximately 4 to 6 weeks before parturition and results in colostral IgG concentrations in first milking colostrum that are several-fold higher than maternal serum concentrations. This active IgG transfer ceases suddenly at the onset of lactation, presumably in response to increased prolactin secretion around parturition.[2] IgA and IgM are largely derived from local synthesis by the mammary gland rather transfer from plasma.

Following ingestion by the newborn, a significant proportion of these immunoglobulins is transferred across the epithelial cells of the small intestine during the first few hours of life and transported via the lymphatic system to the blood. Immunoglobulins in blood are further varyingly distributed to extravascular fluids and to body secretions depending on the immunoglobulin class.

These absorbed immunoglobulins protect against systemic invasion by microorganisms and septicemic disease during the neonatal period. Unabsorbed immunoglobulins and immunoglobulins resecreted into the gut play an important role in protection against intestinal disease for several weeks following birth. FTPI has unequivocally been associated with increased morbidity and mortality and reduced growth rates of neonates. Adequate immunoglobulin supply at birth is associated with higher first- and second-lactation milk production and decreased risk of culling during the first lactation.[5]

In foals, FTPI presents a significant risk for the development of illness during the first 3 months of life.

Lactogenic Immunity

The IgG concentration in milk falls rapidly following parturition in all species, and immunoglobulin concentrations in milk are low (Table 19-3). In the sow, the concentration of IgA falls only slightly during the same period, and it becomes a major immunoglobulin of sows' milk. IgA is synthesized by the mammary gland of the sow throughout lactation and serves as an important defense mechanism against enteric disease in the nursing piglet. IgA in milk is an important mucosal defense mechanism in piglets, whereas in the calf there is little IgA in milk, but some enteric protection is provided by colostral and milk IgG and IgG derived from serum that is resecreted into the intestine.

FAILURE OF TRANSFER OF PASSIVE IMMUNITY

FTPI is the major determinant of septicemic disease in most species. It also modulates the occurrence of mortality and severity of enteric and respiratory disease in early life and performance at later ages.

In terms of the modulation of disease, there can be no set cut-point for circulating immunoglobulins because this cut-point will vary according to the farm, its environment, infection pressure, and the type of disease. Values are given as guidelines. **FTPI in calves** has been defined as a **serum IgG concentration below 1000 mg/dL (10 mg/mL)** when measured between 24 hours and 7 days of age. With **foals**, the equivalent IgG cutoff concentrations **for FTPI** and **partial FTPI are given as 400 mg/dL** and **800 mg/dL**, respectively. Although a serum IgG concentration above 400 mg/dL might be adequate for healthy foals kept in a clean environment with minimal pathogen exposure, a concentration above 800 mg/dL is considered optimal.[6] For **New World camelid crias,** a cut-point value for the serum IgG concentration **of 1000 mg/dL** measured at around 36 hours of life has been recommended.[7]

Rates of FTPI in dairy calves can vary widely between farms, but they were estimated to be in the range of 20% in a recent nationwide survey conducted in the United States.[1] In beef calves FTPI rates tend to be lower; a recent Canadian study reported the incidence of FTPI, defined as serum IgG concentrations below 800 mg/dL, of 6% and a rate of marginal transfer of passive immunity (800 mg/dL < IgG < 1600 mg/dL) of 10%.[8] Failure rates in foals reported in the literature are approximate 13% to 16%. Rates in lambs are also comparatively low, and the incidence of FTPI in crias has been estimated to be around 10%.[7]

In animals that are **fed colostrum artificially**, risk for FTPI is primarily dependent on the amount or mass of immunoglobulin present in a feeding of colostrum, the time after birth that this is fed, the efficiency of its absorption from the digestive tract, and possibly also the degree of bacterial contamination.[1] The mass of immunoglobulins fed is determined by the concentration of immunoglobulin in the colostrum and the volume that is fed. Feeding trials with calves suggest that a **mass of at least 150 g** of IgG is required in colostrum fed to a 45-kg calf to obtain adequate (≥1000 mg/dL IgG) colostral immunoglobulin concentrations in serum.

In animals that **suck colostrum naturally**, such as foals, risk for FTPI is primarily dependent on the concentration of immunoglobulin in the colostrum, the amount that is ingested, and the time of first suckling. Inadequate colostral immunoglobulin concentration and delay in ingestion of colostrum are the two important factors in FTPI in foals.

DETERMINANTS OF TRANSFER OF COLOSTRAL IMMUNOGLOBULINS

1. Amount of immunoglobulin in colostrum fed:
   a. *Volume* of colostrum fed
   b. *Concentration* of immunoglobulins in colostrum
2. Amount of colostrum actually suckled or fed
3. Rate of abomasal or gastric emptying after colostrum ingestion
4. Efficiency of absorption of immunoglobulins by neonate
5. Time after birth of suckling or feeding
6. Time of collection of colostrum after calving (with artificial colostrum feeding)
7. Degree of bacterial contamination of colostrum

Table 19-3 Failure of transfer of passive immunity;[1] concentrations and relative percentage of immunoglobulins in serum and mammary secretions of cattle and pigs

		CONCENTRATION (mg/ml)			TOTAL IMMUNOGLOBULIN (%)		
Animal	Immunoglobulin	Serum	Colostrum	Milk	Serum	Colostrum	Milk
Cow	IgG_1	11.0	75.0	0.59	50	81	73
	IgG_2	7.9	2.9	0.02	36	5	2.5
	IgM	2.6	4.9	0.05	12	7	6.5
	IgA	0.5	4.4	0.14	2	7	18
Sow	IgG	21.5	58.7	3.0	89	80	29
	IgM	1.1	3.2	0.3	4	6	1
	IgA	1.8	10.7	7.7	7	14	70

Determinants of Immunoglobulin Concentration in Colostrum

Nominal concentrations of immunoglobulin in the first milking colostrum of cows and sows are shown in Table 19-4.[1] Current conventional wisdom posits that **high-quality bovine colostrum** should contain **at least 50 g/L IgG**,[2] and that 3 L of high-quality colostrum should be fed as soon as possible after birth.[3,4] This strategy will provide the needed 150 g of colostral IgG. There can be substantial variation in the concentration of immunoglobulin in colostrum in all species, and the ingestion of a "normal" amount of colostrum that has low immunoglobulin concentration may provide an insufficient amount of immunoglobulin for protection. In a study of over 900 first-milkings colostrum from Holstein Friesian cows, only 29% of the colostrum samples contained a sufficiently high concentration of immunoglobulin to provide 100 g IgG in a 2-L volume. The equivalent percentages for 3- and 4-L volume feedings were 71% and 87%, respectively.

It is apparent that variation in colostral immunoglobulin concentration can be a cause of FTPI. Some causes of this variation are the following:

- The concentrations of immunoglobulin in colostrum fall dramatically after parturition. The concentrations in second-milking colostrum are approximately half those in the first milking, and by the fifth postcalving milking, concentrations approach those found during the remainder of lactation. A similar situation exists with **horses**. The mean concentrations of IgG in colostrum of mares 3 to 28 days before foaling is greater than 1000 mg IgG/dL, whereas at parturition the mean concentrations may vary from 4000 to 9000 mg/dL. The concentrations decrease markedly to 1000 mg/dL in 8 to 19 hours after parturition.
- The immunoglobulin concentration of colostrum decreases after calving even when the cow is not milked. It is important that this colostrum be **milked as soon as possible after parturition.** Colostrum that is collected 6 hours or later after calving has a significantly lower concentration than that collected 2 hours after calving. In a study documenting the effect of time since parturition on colostral IgG concentration, it was observed that colostral IgG concentration decreased by 3.7% during each subsequent hour after calving because of postparturient secretion of IgG-poor milk by the mammary glands.
- Colostrum from cows or mares that have been **premilked** to reduce udder edema or from dams that **leaked colostrum** before parturition have low immunoglobulin concentrations, and alternate colostrum should be fed for immunoglobulin transfer.
- In cattle, **dry periods** of less than 30 days may result in colostrum of lower immunoglobulin concentration.
- **Premature foaling** or the **induction of premature parturition** using long-acting corticosteroids in cattle can result in colostrum with low immunoglobulin concentration and/or low volume.
- In cattle, average colostral immunoglobulin concentrations are higher in cows in third or higher **lactation groups** compared with younger cows. However, colostrum from all lactation numbers can produce adequate immunoglobulin mass. There is no scientific basis for not feeding first-milking colostrum from first-lactation cows.
- Larger-volume first-milking colostrum tends to have lower immunoglobulin concentrations than smaller-volume colostrum, presumably as a result of dilution.
- Immunoglobulin concentrations were found to be higher in the early temporal fractions of a single milking of first-milking colostrum. This might suggest that segregation of the first portion of the first-milking colostrum could provide colostrum with higher immunoglobulin concentration for feeding.
- There are **breed differences** in the concentration of immunoglobulins in first-milking colostrum. In **cattle**, beef breeds have higher concentrations. Many dairy breeds, including Holstein Friesian, produce colostrum of relatively low immunoglobulin concentration, and a significant proportion of calves that suckle cows of these breeds ingest an inadequate mass of immunoglobulin. Channel Island breeds have a greater concentration of immunoglobulin in colostrum that Holstein Friesians. **Breed differences** are also seen in **horses**, with Arabian mares having higher colostral immunoglobulin concentrations than Standardbreds, which in turn are higher than those of Thoroughbreds. Breed differences also occur in **sheep**, with higher concentrations in meat and wool breeds than dairy breeds.
- Heat **stress** to cattle in the latter part of pregnancy results in lower colostral immunoglobulin concentrations.
- Colostral volume but not colostral immunoglobulin concentration is reduced in mastitic quarters, and it is unlikely that mastitis is a major determinant of the high rate of FTPI in dairy calves. Colostrum from cows with clinical mastitis should nonetheless not be fed because it may contain pathogens in large amounts and has unphysiologic composition.
- The **pooling of colostrum** in theory could avoid the variation in immunoglobulin concentration of individually fed colostrum and could provide a colostrum that reflects the antigenic experience of several cattle. In practice, colostrum pools from Holsteins invariably have low immunoglobulin concentrations because high-volume, low-concentration colostrum dilutes the concentration of the other samples in the pool. If pools are used, the diluting influence of low-immunoglobulin-concentration, high-volume colostrum should be limited by restricting any individual cow's contribution to the pool to 9 kg (20 lb) or less. However, pooling increases the risk of disease transmission because multiple cows are represented in a pool and the pool is fed to multiple calves. This can be important in the control of Johne's disease, bovine leukosis, *Mycoplasma bovis*, *E. coli*, and *Salmonella* spp.
- **Bacterial contamination** of colostrum can have a negative effect on transfer of passive immunity. The current recommendation is that fresh colostrum should contain less than 100,000 cfu/mL total bacteria count and less than 10,000 cfu total coliform count.[2] One study found that 85% of colostrums sampled from 40 farms in the United States exceeded this threshold. Colostrum that is to be fed or stored should be collected with appropriate preparation and sanitation of the cow and of the milking equipment used on fresh cows.
- **Pasteurization of colostrum** either at 63° C (145° F) for 30 min or 72° C (162° F) for 15 s was shown to reduce colostrum IgG concentration by at least 30% and to thicken or congeal the colostrum. In contrast, **pasteurization at 60° C (140° F) for 60 min** was found to affect neither colostral IgG concentration nor fluid characteristics while eliminating or at least significantly decreasing the content of major pathogens, including *Mycobacterium avium subps. paratuberculosis*, *M. bovis*, *E. coli*, and *Salmonella* spp.
- **Old mares** (older than 15 years) may have poor colostral immunoglobulin concentration.

Volume of Colostrum Ingested

Dairy Cows

The volume of colostrum that is fed has a direct influence on the mass of immunoglobulin ingested at first feeding. The average volume of colostrum ingested by nursing Holstein Friesian calves in the first 24 hours of life is reported as 2.4 L, but there is wide variation around this mean. In **natural suckling** situations, calves may fail to ingest

adequate colostrum volumes before onset of the closure process and therefore absorb insufficient colostral immunoglobulin. Early assisted suckling may help avoid this. In dairy calves the volume of colostrum that is ingested can be controlled in **artificial feeding systems** using nipple bottle feeders or esophageal tube feeders. **Bucket feeding** of colostrum is not recommended because training to feed from a bucket can be associated with erratic intakes.

The **traditional recommendation** for the volume of colostrum to feed at first feeding to calves is 2 L (2 quarts). However, only a small proportion of first-milking colostrum from Holsteins contains a sufficiently high concentration of immunoglobulin to provide 100 g IgG in a 2-L volume, and higher volumes of colostrum are required to achieve this mass intake. Some calves fed with a **nipple bottle** will drink volumes greater than 2 L, but others will refuse to ingest even 2 L of colostrum in a reasonable period of time, and calf rearers may lack the time or patience to persist with nipple bottle feeding until the required volume has been ingested by all calves.

Larger volumes of colostrum can be fed by an **esophageal feeder,** and single feedings of large volumes of colostrum (3.5 to 4.0 L per 45 kg of body weight) result in the lowest percentage of calves with FTPI by allowing calves fed colostrum with relatively low immunoglobulin concentrations to receive an adequate immunoglobulin mass before closure. Feeding this volume by an esophageal feeder causes no apparent discomfort to a minimally restrained calf and was not found to negatively affect intestinal IgG absorption compared with voluntary intake of the same (large) volume.[10] There is nonetheless some debate around the recommendation to systematically tube feed neonatal calves because of animal welfare concerns. In several European countries animal welfare legislation prohibits force-feeding of animals without medical indication.[20]

Beef Cows

With beef breeds very effective colostral immunoglobulin transfer is achieved with natural sucking. This is thought to be a result of the greater vigor at birth exhibited by these calves and the higher immunoglobulin concentrations in beef colostrum, requiring a smaller volume intake to acquire an adequate mass. **Natural sucking** will give an adequate volume intake, and there is no need to artificially feed colostrum unless the dam is observed to refuse nursing or the calf's viability and sucking drive are compromised. The **yield of colostrum** and colostral immunoglobulins in beef cows can vary widely, and range beef heifers may produce critically low volumes of colostrum. Differences in yield can be attributed to breed or to nutritional status, although undernutrition is not an effect unless it is very severe.

Ewes

Colostrum yield is high in ewes in good condition at lambing, but it may be low in ewes with condition scores of 1.5 to 2.0.

Sows

In sows there is also very effective colostral immunoglobulin transfer with natural sucking, and piglets average an intake of 5% to 7% of body weight in the first hour of life. There is between-sow variation in the amount of colostrum, and there can be a large variation in colostrum supply from teat to teat, which may explain variable health and performance. During farrowing and for a short period following, colostrum is available freely from the udder, but thereafter it is released in ejections during mass suckling. A strong coordinated sucking stimulus is required by the piglet for maximum release of colostrum, and this requires that the ambient temperature and other environmental factors be conducive to the optimum vigor of the piglets. Small-birth-weight piglets, **late-birth-order** piglets, and piglets sucking posterior teats obtain less colostrum.

All Species

In all species a low-volume intake may also occur because of the following factors:

- Poor **mothering behavior**, which may prevent the newborn from sucking; occurrence of disease; or milk fever
- Poor **udder and/or teat conformation** so that the newborn cannot suck normally or teat seeking is more prolonged. Udder-to-floor distance is most critical, and low-slung udders can account for significant delays in intake. Bottle-shaped teats (35-mm diameter) also significantly reduce intake.
- Delayed and **inadequate colostral intake** frequently accompanies perinatal asphyxia or acidemia because of the greatly decreased vigor of the calf in the first few hours of life. Perinatal asphyxia can occur in any breed and is greatly increased by matings resulting in fetal–maternal disproportion and dystocia.
- The newborn may be weak, traumatized, or unable to suck for other reasons; a **weak sucking drive** can be a result of congenital iodine deficiency, cold stress, or other factors.
- Disease of the periparturient dam, such as clinical hypocalcemia in cattle or the mastitis metritis agalactia complex in sows, may preclude adequate colostrum intake by offspring.
- Failure to allow newborn animals to ingest colostrum may occur under some management systems.

Efficiency of Absorption

After ingestion of colostrum by the newborn, colostral immunoglobulins are absorbed from the small intestine, by a process of pinocytosis, into the columnar cells of the epithelium. In the newborn calf this is a very rapid process, and immunoglobulin can be detected in the thoracic duct lymph within 80 to 120 minutes of its being introduced into the duodenum. The **period of absorption** varies between species and with immunoglobulin class. The mechanism by which absorption ceases is not well understood, but it may be related to replacement of the fetal enterocyte. The region of maximum absorption is in the lower small intestine, and peak serum concentrations are reached by 12 to 24 hours in all species. Absorption is not limited to immunoglobulin, and **proteinuria** during the first 24 hours of life is associated with the renal excretion of low-molecular-weight proteins such as β-lactoglobulin.

Feeding Methods, "Closure of the Gut," and Immunoglobulin Absorption

Under normal conditions complete loss of the ability to absorb immunoglobulin (closure of the gut) occurs by 24 to 36 hours after birth in all species, and there is a significant reduction in absorptive ability (as much as 50% in some studies but minimal in others) by 8 to 12 hours following birth. The **time from birth to feeding** is a crucial factor affecting the absorption of colostral immunoglobulin in all species, and any delay beyond the first few hours of life, particularly after 8 hours, significantly reduces the amount of immunoglobulin absorbed.

The recommendation is that all neonates should be fed colostrum within the first 2 hours of life.

Natural Sucking

Natural sucking is the desired method of intake of colostrum and is the most efficient, but it is influenced by the sucking drive and **vigor** of the neonate at birth. Newborns that suck colostrum can achieve very high concentrations of colostral immunoglobulin, and the efficiency of absorption is best with this feeding method. However, in dairy calves natural sucking is commonly associated with a high rate of FTPI because of **delays in sucking** coupled with low intake. Rates of FTPI in calves allowed to obtain colostrum via voluntary nursing reported in the literature can be as high as 40% to 60%.[1] Many factors influence the occurrence of delayed sucking, but calf vigor and birth-related asphyxia are the most important. Parity of the dam, conformation of the udder, and breed were also found to be significantly associated with the rate of FTPI. One older study reported that 46% of all calves born to multiparous cows had failed to nurse within 6 hours of birth compared with 11% of calves of primiparous cows.[11] Jersey calves have better rates of successful transfer of passive immunity with natural sucking than do Holsteins Friesians.

Artificial Feeding

In contrast, when calves are **fed colostrum artificially**, minimal delays from birth to the time of colostrum feeding occur, and maximal colostrum immunoglobulin absorption results. In breeds such as Holstein Friesians, where colostral immunoglobulin concentrations tend to be low and maximal efficiency of absorption is necessary, the logical way to minimize risk of FTPI is to feed the maximum volume of colostrum that is well tolerated within the first few hours of life. The published literature consistently reports higher calf serum IgG concentrations and a lower rate of FTPI in response to larger colostrum feeding volumes.[2,10,12]

Other Influences

Even with the best available on-farm colostrum-selection methods, **large colostrum-feeding volumes are essential** to minimize the risk of FTPI in breeds with relatively low colostral immunoglobulin concentrations. The method is particularly advantageous where time constraints of other farm activities limit the time available for calf feeding. The major detrimental influence on absorptive efficiency of immunoglobulin is **delayed feeding after birth**. Other factors that may affect absorptive efficiency include the following:

- **Perinatal asphyxia or acidemia** may have both direct and indirect effects on colostral immunoglobulin transfer. Asphyxia has a major effect on subsequent sucking drive, and acidemic calves ingest far less colostrum than calves with more normal acid–base status at birth. In carefully controlled colostrum feeding studies, a significant negative correlation between the degree of hypercapnia and the efficiency of absorption of colostral immunoglobulin in the first hours of life was demonstrated. However, this effect was only transient because there was no difference in serum IgG concentration at the time of gut closure between normoxic and hypoxic calves.
- In one early study, a **mothering effect** was reported in which calves remaining with their dams absorbed colostral immunoglobulin more efficiently than calves removed immediately to individual pens. However, other studies have shown much smaller or no effects of mothering using similar experimental designs. The different results of these studies have not been reconciled.
- There can be **seasonal** and **geographic** variations in transfer of immunoglobulin in calves, although these are not always present on farms in the same area, and their cause is unknown. Where seasonal variation occurs in temperate climates, the mean monthly serum IgG concentrations are lowest in the winter and increase during the spring and early summer to reach their peak in September, after which they decrease. The cause is not known, but a decrease in sucking drive is observed in colder months and may contribute. In subtropical climates, peak levels occur in the winter months, and low levels are associated with elevated temperatures during the summer months. **Heat stress** in late pregnancy will reduce colostral immunoglobulin concentration, but high ambient temperature is a strong depressant of absorption, and the provision of shade will help to obviate the problem.
- The efficiency of absorption may be decreased in **premature calves** that are born following induced parturition using long-acting corticosteroids; in contrast, medical **induction of parturition** with short-acting corticosteroids in cattle does not interfere with the efficiency of absorption of immunoglobulins in calves.
- The absorption of small volumes (1 to 2 L) fed by an esophageal feeder is usually suboptimal and inferior to the absorption after sucking the same small volume.[10] This effect may at least in part be attributable to retention of some colostrum in the immature forestomaches for several hours. The calf will feel satiated and not inclined to suck naturally for the next few hours.
- A **trypsin inhibitor** in colostrum may serve to protect colostral IgG from intestinal degradation. It varies in concentration between colostrums. The addition of a trypsin inhibitor to colostrum improves immunoglobulin absorption.
- In a study of **mare-associated determinants of FTPI** in foals (based on serum Ig measurements), there was a trend to increase rates of FTPI in foals from mares aged over 12 years, but no significant association with age, parity, or gestational age of foals over 325 days was found. There was an association with season, with a lower incidence in the late spring compared with foals born earlier in the year and with a foal score based on a veterinary score of foal health and "fitness."

Traditionally it has been considered that the **movement** of animals, either the dam just **before parturition** or the newborn animal during the first few days of life, is a special hazard for the health of the calf. The postulated reason is that the dam may not have been exposed to pathogens present in the new environment and thus not have circulating antibodies against these pathogens. The newborn animal may be in the same position with regard to both deficiency of antibodies and exposure to new infections. Although this may be the case in some situations, the developing practice of contract-rearing of dairy heifers away from the farm to be brought back as close-up springers and the practice of purchase of close-up heifers on the farm are not associated with appreciable increase in mortality in their calves.

Decline of Passive Immunity

Colostral antibody concentrations in blood fall quickly after birth and have usually disappeared by 6 months of age. In the **foal**, they have fallen to less than 50% of peak level by 1 month of age and to a minimum level between 30 and 60 days. This is the point at which naturally immunodeficient foals are highly susceptible to fatal infection.

In **calves**, the level of IgG declines slowly and reaches minimum values by 60 days, in contrast to IgM and IgA, which decline more rapidly and reach minimum values by approximately 21 days of age. The half-lives for IgG, IgM, and IgA in calves are approximately 20, 4, and 2 days, respectively, and the half-lives of IgGa, IgGb, IgG(T), and IgA in foals are approximately 18, 32, 21, and 3.5 days, respectively.

Immunologic competence is present at birth, but endogenous antibody production does not usually reach protective levels until 1 month, and maximum levels are not reached until 2 to 3 months of age. The endogenous production of intestinal IgA in the piglet begins at about 2 weeks of age and does not reach significant levels until 5 weeks of age.

Foals that acquire low concentrations of immunoglobulins from colostrum may experience a transitory hypogammaglobulinemia at several weeks of age as the levels fall and before autogenous antibodies develop. They are, as expected, more subject to infection than normal.

OTHER BENEFITS OF COLOSTRUM

In addition to its immunoglobulin content, colostrum contains considerably more protein, fat, vitamins, and minerals than milk and is especially important in the transfer of fat-soluble vitamins. It has **anabolic effects,** and lambs that ingest colostrum have a higher summit metabolism than colostrum-deprived lambs. Colostrum also contains growth-promoting factors that stimulate DNA synthesis and cell division, including high concentrations of insulin-like growth factor (IGF)-1.

Colostrum contains approximately 1×10^6 leukocytes/mL, and several hundred million are ingested with the first feeding of colostrum. In calves, 20% to 30% of these are lymphocytes and cross the intestine into the circulation of the calf. It is postulated that they have importance in the development of neonatal resistance to disease, but there is little tangible evidence. Calves fed colostrum depleted of leukocytes are thought to be more poorly protected against neonatal disease than those fed normal colostrum.

ASSESSMENT OF TRANSFER OF PASSIVE IMMUNITY

Because of the importance of transfer of colostral antibodies to the health of the neonate, it is common to quantitatively estimate the levels of immunoglobulins, or their surrogates, in colostrum and in serum to predict risk of disease and to take preventive measures in the individual or to make corrective management changes where groups of animals are at risk.

Assessment in the Individual Animal

When samples are taken from an individual animal to determine the risk for infection, sampling is undertaken early so that replacement therapy can be given promptly if there has been inadequate transfer. IgG is detectable in serum 2 hours following a colostrum feeding and **sampling at 8 to 12 hours** after birth will give a good indication of whether early sucking has occurred and has been effective in transfer. This type of monitoring is commonly performed in foals and camelid crias.[7,13] There are a number of different tests that can be used; some are quantitative and others semiquantitative. In calves, sampling may be undertaken for similar reasons, but the cost of replacement therapy is limiting.

Assessment Tests on Serum

Sampling to **monitor** the efficacy of a farm policy for feeding and handling colostrum, to evaluate the passive immunity status in **calves to be purchased,** or to determine the **rates of FTPI** in investigations of neonatal disease can be conducted at any time in the first week of life after 24 hours with most tests. Numerous tests are currently available, some of which directly measure serum IgG concentration and some of which estimate the IgG concentration based on the serum concentration of the total globulin or other protein fractions.

Radial Immunodiffusion

The radial immunodiffusion (RID) is based on the precipitation of antigen and antibody to an insoluble precipitin complex and thus directly measures IgG concentration in serum or plasma. The RID is considered the reference method to measure serum/plasma IgG, but it takes at least 24 h to perform and thus longer than is desirable for most clinical purposes. In a recent study two commercial RID test kits for calves were compared, and a large bias and wide limits of agreements between the two tests were found, which has raised questions about the reliability of the results.[21]

Lateral-Flow Immunoassay

The lateral-flow immunoassay is a calf-side test directly measuring IgG in serum or plasma with reportedly high sensitivity and specificity. Although the test can be performed on-site and results are available within 20 min, it only provides a pass/fail result using a cutoff value of 10 mg/mL.[2]

Turbidimetric Immunoassay

The turbidimetric immunoassay (TIM) is commercially available and can be run on a handheld chemistry analyzer to be used with bovine serum. In a preliminary study conducted at the University of Minnesota, the test was found to be more accurate than indirect tests such as serum refractometry.

Zinc Sulfate Turbidity Test

The zinc sulfate turbidity test is based on a selective precipitation reaction of the salt with high molecular weight proteins such as immunoglobulin (not specifically IgG). The test is commonly used with a test solution containing 200 mg/L zinc sulfate but was found to have poor specificity and would only classify 69% of tested calves correctly. Increasing the zinc sulfate concentration from 200 to 350 mg/L considerably improved the specificity and positive predictive values of the test, but this test modification is not widely used.[15] Another inconvenience is that hemolyzed blood samples will give artificially high readings, and the reagent must be kept free of dissolved carbon dioxide.

Sodium Sulfite Precipitation Test

The sodium sulfite precipitation test is based on the selective precipitation of high-molecular-weight proteins with sodium sulfate at different concentrations. Test solutions of 14%, 16%, and 18% sodium sulfite are commonly used, and the development of turbidity at a certain concentration allows for a crude estimate of the serum immunoglobulin concentration; the lower the concentration at which turbidity occurs, the higher is the concentration of immunoglobulin. Particularly the use of the 14% and 16% sodium sulfite solutions was found to result in an unacceptably high percentage of calves being misclassified as FTPI while having adequate serum immunoglobulin concentrations.[15]

Serum γ-Glutamyltransferase Activity

Serum γ-glutamyltransferase (GGT) activity has been used as a surrogate for determining the efficacy of transfer of passive immunity in calves and lambs (not in foals). GGT activity is high in the colostrum of ruminants (but not horses), and serum GGT activity in calves and lambs that have sucked or been fed colostrum is 60 to 160 times greater than normal adult serum activity and correlates moderately well with serum IgG concentrations. The half-life of GGT from colostrum is short, and serum GGT activity falls significantly in the first week of life. Serum GGT values equivalent to a serum IgG concentration of 10 mg/mL are 200 IU/L on day 1 of life and 100 IU/L on day 4. Serum GGT concentrations less than 50 IU/L indicate FTPI.

Serum Total Protein

Measuring total protein concentrations in serum or plasma with a refractometer is a practical, rapid, and inexpensive method to estimate the immunoglobulin concentration by extrapolating it from the total protein concentration. Despite the indirect nature of the test, there is a reliable correlation between the refractometer reading and total immunoglobulin concentration measured by RID. In healthy calves a serum total protein of 5.5 g/dL or greater is associated with adequate transfer of passive immunity.

Serum total protein has a good predictive value for fate of the newborn, and the facile and practical nature of the test and its predictive ability commend it for survey studies in calves and lambs but not foals. Cut-points will vary with the environment and the infection pressure to the calves. The sensitivity of the test is maximal using a cut-point of 5.5 g/dL, and the specificity is maximal at a cut-point of 5.0 g/dL. Because serum total protein concentration measured by refractometry can result in an incidental misclassification of an individual calf, this test is primarily recommended as a screening tool to assess the colostrum management on a herd level, but not as diagnostic tool for an individual animal. Herd screening could be conducted by testing a minimum of 12 calves on a farm between 24 hours and 7 days old. At least 80% of tested calves should have serum protein concentrations above 5.5 g/dL to consider the colostrum management satisfactory at the herd level.

Serum total protein concentration can also be estimated using the same Brix refractometer used for measuring colostral IgG concentration, with an appropriate adjustment factor.[14]

Glutaraldehyde Coagulation Test

The glutaraldehyde test was initially introduced to identify hypergammaglobulinemia in adult cattle with chronic inflammatory disease. The semiquantitative test is based on a clotting reaction of glutaraldehyde in the presence of high immunoglobulin concentration, where the time to clot formation is negatively correlated with the serum IgG.[16] A modified glutaraldehyde coagulation test is also available for the detection of hypogammaglobulinemia in neonatal calves, but it is less accurate.[15] The test may yield false-positive results with hemolysis and is difficult to quantitate.

Latex Agglutination Test

A commercial latex agglutination test is available for horses. It is rapid and provides semiquantitative results, but results were reported to be inconsistent.

ELISA Snap-Test

ELISA snap-tests are foal-side immunologic tests directly measuring IgG in a

semiquantitative manner. Test kits are commercially available for foals and have been available for calves. In foals the available snap-tests were found to be rapid and accurate.

Monitoring Colostrum

Brix Refractometry

The most accurate and practical way to ensure that an adequate colostral mass is fed is to test the colostrum using a Brix refractometer (the digital version is preferred). This instrument was designed for use in food processing but was adapted in the late 1970s to provide a low-cost test of colostrum quality. A Brix refractometer value of 21% or 22% or higher indicates acceptable colostrum (same value for fresh or frozen samples; approximately equivalent to a colostral IgG concentration of 50 g/L); colostrum with a value below 21% or 22% should be discarded.[17,18]

Specific Gravity

Specific gravity, determined by refractometry, can be used as a measure of the immunoglobulin content of colostrum. In **mares** the concentration of immunoglobulin in colostrum is highly correlated with the specific gravity of the colostrum, which in turn is highly correlated with the serum immunoglobulin levels achieved in foals. Temperature-corrected measurements are most accurate. Measurement of colostrum specific gravity provides a rapid and easy method of identifying foals likely to be at a high risk for FTPI and the need to provide them with colostrum of a higher Ig content. To prevent FTPI, it is recommended that the colostral specific gravity should be equal to or greater than 1.060, and the colostral IgG concentration should be a minimum of 3000 mg/dL.

In **cattle** the relation of specific gravity of colostrum to colostral immunoglobulin concentration is linear but is better in Holstein Friesian than in Jersey cows. The measurement is simple, but there is a correction for temperature, and air trapped in colostrum taken by a milking machine can give a false reading if the measurement is taken too quickly after milking. The cut-point recommended to distinguish moderate from excellent colostrum has been set at 1.050, approximating an IgG concentration of 50 g/L, and is based on the amount of immunoglobulin required for a 2-L (2-quart) feeding. Specific gravity is not a perfect surrogate for immunoglobulin concentration with cattle colostrum. It has good negative prediction, but it will falsely pass 2 out of 3 colostrums that have unacceptably low immunoglobulin concentrations. An analysis of first-milking colostrum in midwestern U.S. dairies found that specific gravity differed among breeds and was influenced by month of calving, year of calving, lactation number, and protein yield in previous lactation and that it was more closely associated with colostrum protein concentration ($r = 0.76$) than IgG_1 concentration ($r = 0.53$).

Glutaraldehyde Test

This test for mare colostrum is available commercially and is reported to have a high predictive value for colostrums that contain more than 38 mg/mL of IgG and have a specific gravity greater than 1.060.

ELISA

Recently a cow-side immunoassay kit has become available commercially in the United States. The kit provides a positive or a negative response, with the cut-point being a concentration of 50g/L of IgG in colostrum, and has accuracy sufficient to recommend its use for rejection of colostrums with low immunoglobulin concentration.

CORRECTION OF FAILURE OF TRANSFER OF PASSIVE IMMUNITY

Oral Therapy

Oral therapy can be considered in individual animals (generally foals and crias), provided that FTPI—or the risk thereof—is diagnosed and the treatment is administered before gut closure (i.e., not later than 18 h of life). For foals, oral administration of at least 0.5 L frozen equine colostrum of good quality (specific gravity > 1.060) that has been properly stored and thawed is recommended. Alternatives include colostrum substitutes containing lyophilized IgG or good-quality bovine colostrum. The latter option is probably the least effective and requires at least 4 L of good-quality (specific gravity >1.050) colostrum.

Parenteral Immunoglobulins

Blood transfusion is commonly used in food animal practice, and the method is described elsewhere in this text. Fresh plasma from a random donor or purified hyperimmune plasma that is commercially available for foals and crias in some countries are alternatives. Large amounts are required to obtain the required high serum concentrations of immunoglobulins, and intravenous infusion can be accompanied by transfusion-type reactions.

AVOIDANCE OF FAILURE OF TRANSFER OF PASSIVE IMMUNITY

With all species, with the exception of dairy calves, the common practice is to allow the newborn to suck naturally. The policy for avoidance of FTPI with naturally sucking herds should be to provide supplemental colostrum by artificial feeding of those neonates with a high risk for FTPI, based on the risk factors detailed earlier. In the dairy calf, rates of FTPI with natural sucking are so high that many farms opt to remove the calf at birth and feed colostrum by hand to ensure adequate intake.

Colostrum

Colostrum can be stripped from the dam and fed fresh, or the neonate can be fed stored (banked) colostrum.

Colostrum for Banking

With **dairy cows**, first-milking colostrum from a cow with a first-milking yield of less than 10 kg should be used. The temptation for the farmer is to store the leftover from the feeding of large-volume colostrum. The leftover colostrum should not be used because it has a high probability of containing a low immunoglobulin concentration.

Colostrum from **mares** should have a specific gravity of 1.060 or more, and 200 mL can be milked from a mare before the foal begins sucking.

Storage of Colostrum

Colostrum can be kept at **refrigerator temperature** for approximately 1 week without significant deterioration in immunoglobulins; bacteria counts, however, may reach unacceptably high levels (above 100,000 cfu/mL) after 2 days in refrigerated milk.[2] Addition of potassium sorbate in a 0.5% final solution impairs bacterial growth for several days.[2] The addition of 5 g of propionic or lactic acid per liter extends the storage life to 6 weeks, but, more commonly, colostrum is frozen for storage. **Frozen colostrum**, at −20° C (−4° F), can be stored for at least 1 year, and there is no impairment in the subsequent absorption of immunoglobulins. Frozen colostrum should be stored in flat plastic bags in the amount required for a feeding, which facilitates thawing. **Thawing** should be at temperatures below 55° C (131° F). Higher temperatures and microwave thawing result in the deterioration of immunoglobulins and antibodies in frozen colostrum and frozen plasma.

Pasteurization of Colostrum

There are several indications for pasteurization of colostrum. This procedure can be a suitable instrument in a program for the control of specific infectious diseases, such as paratuberculosis, salmonellosis, or *M. bovis* infection, but it can also be useful to ameliorate calf health by improving colostrum quality and reducing the exposure of the neonate to pathogens. On-farm pasteurization of bovine colostrum for 60 min at 60° C (140° F) results in elimination or at least significant reduction of bacterial contamination without impairing fluid characteristics or availability of IgG for intestinal absorption.[9] One recent study reported significantly higher serum IgG concentrations at 24 h of life when calves were fed pasteurized colostrum compared with calves receiving the same quality and amount of raw colostrum.[19] The authors attributed this effect to reduced bacterial interference with intestinal IgG absorption. Pasteurization extends the shelf life of refrigerated colostrum without

additives to 8 to 10 days when stored in clean, sealed containers.

Cross-Species Colostrum

Colostrum from another species can be used to provide immunologic protection when same-species colostrum is not available. Bovine colostrum can be fed to a number of different species. Although absorption of immunoglobulin occurs and significant protection can be achieved, the use of cross-species colostrum is not without risk, and the absorbed immunoglobulin has a short half-life. Bovine colostrum has been successfully used for many years to improve the survival rate of hysterectomy-produced artificially reared pigs. It has also been used as an alternate source of colostral antibody for rearing goats free of caprine arthritis–encephalitis (CAE). Colostrum from some cows can result in the development of hemolytic anemia, occurring at around 5 to 12 days of age, in lambs and kids because the IgG of some cows attaches to the red cells and their precursors in bone marrow, resulting in red cell destruction by the reticuloendothelial system. Bovine colostrum can be tested for "antisheep" factors by a gel precipitation test on colostral whey, but this test is not generally available. Bovine colostrum can provide some protection to newborn foals against neonatal infections, and protection appears to result from factors in addition to the immunoglobulins, which have a short half-life in foals.

Colostrum Supplements

In recent years there has been a move to develop supplements or even replacements for colostrum to feed calves. These have been attempted using IgG concentrated from bovine colostrum, milk whey, eggs, or bovine serum. The search for colostrum substitutes or colostrum replacers has been prompted by the problem of the variability of IgG concentration in natural colostrum. It has also been prompted by possible limitations of availability of high-quality colostrum on dairy farms as a result of discarding colostrum from cows that test positive for diseases that can transmit through colostrum, such as paratuberculosis, bovine leukosis, and *M. bovis.*

There is evidence that the inclusion of **colostrum replacer (CR)** or **colostrum supplement (CS)** products can impair the efficiency of colostral immunoglobulin, and if they are fed, they should be fed after normal colostrum rather than mixed into the colostrum. It has been proposed that the distinction between a colostrum supplement and a colostrum replacer should be the immunoglobulin mass contained in the product, with a colostrum supplement containing less than 100 g IgG per dose and a colostrum replacer having sufficient immunoglobulin mass in a dose to result in a serum IgG concentration greater than 10 mg/mL following a feeding. Furthermore, CR products are formulated to provide adequate protein, energy, minerals, and vitamins to completely replace colostrum, which is not the case for CS supplement products. When fed as the sole source of immunoglobulin to colostrum-deprived calves, CS products achieve circulating concentrations of immunoglobulin that are lower than those achieved by natural colostrum containing equivalent amounts of immunoglobulin.

A large mass of immunoglobulin is required for acquisition of adequate serum immunoglobulin concentrations. Calves fed a colostrum replacement containing a high mass (250 g) of an IgG derived from bovine serum and fed at 1.5 and again at 13.5 hours after birth achieved equivalent serum IgG concentrations to calves fed normal colostrum and showed no difference in gain or health parameters during the first 4 weeks of life. However, the performance of commercially available products for IgG supplementation varies greatly, with many of them faring badly. The choice of a specific product should therefore be based on the availability of convincing data supporting the efficacy of the product in question.

The use of colostrum replacers should be limited to situations where sufficient amounts of colostrum of adequate quality are unavailable. There can be little justification for more widespread use, particularly because there are limited independent health-related publications documenting their efficacy. Also, as mentioned earlier, in addition to immunoglobulin, natural colostrum contains various substances important to neonatal physiology.

Lacteal-Secretion-Based Preparations

Colostrum supplements prepared from whey or colostrum are available commercially in many countries. Depending on the manufacturer, they contain varying amounts of immunoglobulin, but significantly less than first-milking colostrum. The amount of immunoglobulin contained varies, but the recommendations for feeding that accompany these products indicate that they will supply approximately 25% or less of the immunoglobulin required to elevate calf serum IgG concentrations above 1000 mg/dL. There is a further problem in that the immunoglobulins in products made from colostrum or whey are poorly absorbed, and trials assessing their ability to increase circulating immunoglobulins when fed with colostrum have generally shown little improvement and no improvement in health-related parameters.

Bovine-Serum-Based Preparations

Colostrum supplements prepared from bovine serum are also available commercially, but regulations governing the feeding of blood or blood products to calves (risk reduction for bovine spongiform encephalopathy) may limit their availability in some countries. The absorption of immunoglobulin from these bovine-serum-derived commercial products appears better than from milk-protein-derived products, and consequently they are also marketed as colostrum replacers.

The IgG in a commercially available bovine serum colostrum replacer has been shown to be effectively absorbed when fed to newborn lambs. The feeding of 200 g of IgG in the first 24 hours of life resulted in a mean plasma concentration of 1800 mg/dL.

Administration of Colostrum

Foals

Foals should be allowed to suck naturally. The specific gravity of the mare's colostrum can be checked at foaling; if this is less than 1.060, supplemental colostrum may be indicated. Foals that do not suck, or that have serum IgG concentrations less than 400 mg/dL at 12 hours of age, or that require supplementation for other reasons, should be fed colostrum with a specific gravity of 1.060 or more at an amount of 200 mL at hourly feedings.

Dairy Calves

Assisted Natural Sucking

Leaving the newborn dairy calf with the cow is no guarantee that the calf will obtain sufficient colostrum, and a high proportion of dairy calves fail either to suck early or to absorb sufficient immunoglobulins from ingested colostrum. This problem can be alleviated to some extent by **assisted natural sucking,** but this can fail because not all calves requiring assistance are detected. An alternate approach is to milk 2 L of colostrum from the dam, bottle feed each calf as soon after birth as possible, then leave the calf with the cow for 24 hours and allow it to suck voluntarily. Although this will not be as effective as a system based entirely on artificial feeding of selected colostrum, it is an approach that is suitable for the smaller dairy farm.

Artificial Feeding Systems

With **artificial feeding systems**, the calf is removed from the dam at birth and fed colostrum by hand throughout the whole absorptive period. Nipple bottle feeding can be used, with 2 L of colostrum given every 12 hours for the first 48 hours of life. The first feeding is usually milked from the cow by hand, and the remaining feedings are from the colostrum obtained from the cow after the first machine milking. With care and patience, this system can result in good transfer of passive immunity in all calves except those born to dams that have very low concentrations of immunoglobulin in their colostrum. Unfortunately, with Holstein Friesians this can be a significant percentage. An extension of this system is to bottle feed at the same frequency but to feed stored

colostrum selected for its superior immunoglobulin content. Bottle feeding of newborn calves requires considerable **patience**, and its success is very much dependent on the calf feeder and on the availability of the feeder's time when faced with a calf that has a slow intake.

Where the diligence of the calf feeders is poor, or where there is a time constraint on their availability, the feeding of a large volume of colostrum (4 L to a 45 kg calf) by **esophageal feeder** at the initial feeding immediately after birth can be a successful practice. The **large-volume feeding** also allows the delivery of an adequate mass of immunoglobulin with colostrum that has low immunoglobulin concentrations without impairing the intestinal IgG absorption rate compared with voluntary intake of the same large amount of colostrum.[10] The practice usually uses stored colostrum, and the feeding can be achieved within a few minutes. It can be supplemented by bottle feeding of a second feeding at 12 hours of life.

The practice of feeding stored colostrum as the sole source of colostrum is limited to larger dairy herds, but it does allow the selection of superior colostrum for feeding, with selection based on weight and specific gravity as detailed earlier.

Beef Calves

Beef calves should be allowed to suck naturally, and force-feeding of colostrum to beef breeds should not be practiced unless there is obvious failure of sucking. Where colostrum is required, as with weak beef calves, calves with edematous tongues, and calves that have been subjected to a difficult birth, it can be administered with an esophageal feeder or a stomach tube.

Lambs

Lambs are allowed to suck naturally, but there can be competition between siblings for colostrum; one large single lamb is capable of ingesting, within a short period of birth, all the available colostrum in the ewe's udder. Lambs require a total of 180 to 210 mL colostrum/kg body weight during the first 18 hours after birth to provide sufficient energy for heat production. This amount will usually provide enough immunoglobulin for protection against infections. **Supplemental feeding** of colostrum may be advisable for lambs from multiple birth litters, lambs that lack vigor, and those that have not nursed by 2 hours following birth. This can be done with a nipple bottle or an esophageal feeder.

Piglets

Colostral supplementation is not commonly practiced with piglets. An immunoglobulin dose of 10 g/kg body weight on day 1 followed by 2 g/kg on succeeding days for 10 days is sufficient to confer passive immunity on the colostrum-deprived pig.

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Clinical Assessment and Care of Critically Ill Newborns

The following discussion focuses on care and treatment of critically ill foals, although the principles are applicable to any species. The increasing availability of secondary and tertiary care for ill newborns has allowed the development of sophisticated care for newborns of sufficient emotional or financial value.[1] This level of care, at its most intensive, requires appropriately trained individuals (both veterinarians and support staff) and dedicated facilities. True intensive care of newborns requires 24-hour monitoring. The following discussion is not a comprehensive guide to intensive care of newborns, but is rather an introduction to the general aspects of advanced primary or basic secondary care. Sophisticated interventions, such as mechanical ventilation and cardiovascular support, are mentioned but not discussed in detail.

CLINICAL EXAMINATION

Initial assessment of an ill newborn should begin with collection of a detailed history, including length of gestation, health of the dam, parturition, and behavior of the newborn after birth, including the time to stand and to commence nursing activity. Physical examination should be thorough, with particular attention to those body systems most commonly affected. A form similar to that in Figure 19-4 is useful in ensuring that all pertinent questions are addressed and that the physical examination is comprehensive.

Examination of ill neonates should focus on detection of the common causes of disease in this age group: sepsis, either focal or systemic; prematurity or dysmaturity; metabolic abnormalities (such as hypoglycemia or hypothermia); birth trauma; diseases associated with hypoxia; and congenital abnormalities. Detailed descriptions of these conditions are provided elsewhere in this chapter.

Sepsis

Sepsis is an important cause of illness in neonates that can manifest as localized infections without apparent systemic signs, localized infections with signs of systemic illness, or systemic illness without signs of localized infection.[2]

Localized infections without signs of systemic illness include septic synovitis or osteomyelitis and omphalitis. Signs of these diseases are evident on examination of the area affected and include lameness, distension of the joint, and pain on palpation of the affected joint in animals with synovitis or osteomyelitis and an enlarged external umbilicus with or without purulent discharge in animals with infections of the umbilical structures. Specialized imaging and hematologic and serum biochemical examinations (see following discussion) are useful in confirming the infection.

Systemic signs of sepsis include depression, failure to nurse or reduced frequency of nursing, somnolence, recumbency, fever or hypothermia, tachypnea, tachycardia, diarrhea, and colic, in addition to any signs of

Foal Examination Protocol (age< 1mon)

The Ohio State University Veterinary Teaching Hospital

Special considerations:

Clinician: _____

Student: _____

Date: _____ Time: _____ AM/PM

History

Mare

Age: ____ No of previous foals: ____ Problems with previous foals? __No __Yes _____

Uterine infections/Vaginal discharge? __No __Yes _____

liiness during pregnancy? __No __Yes _____

Milk dripping? __No __Yes How long? _____

Vaccinations? __No __Yes What/When? _____

Deworming? __No __Yes When? _____

Feeding: _____

Breeding date: _____ Duration of prenancy: _____ → __on term __early __overdue (____days)

Dystocia? __No __Yes _____

Early cord rupture? __No __Yes _____ Premature placental separation? __No __Yes _____

Placenta completely passed? __No __Yes Condition of placenta: _____

Meconium staining? __No __Yes _____

Udder: __Normal __Abnormal _____

Colostrum quality: __Normal __Low-quality _____ Amount: __Normal __Reduced _____

Foal

Spontaneous breathing? __No __Yes _____ Time to stand: _____ Time to nurse: _____

Nursing normally? __No __Yes _____ Colostrum/Milk given? _____

Behavior normal? __No __Yes _____ IgG tested? __No __Yes _____

Urination? __No __Yes _____ Meconium passed? __No __Yes _____ Enema given? __No __Yes _____

Medications given? __No __Yes _____

Umbilicus treated? __No __Yes _____

Presenting complaint: _____

_____

_____

Previous treatment: _____

The Ohio State University
Form–209046

Foal Examination Protocol

Fig. 19-4 Examples of forms used to document and record historical aspects and findings on physical examination of foals less than 1 month of age.

Continued

Physical Examination Date: _____ Time: _____AM/PM

Temperature: _____ºF Pulse rate: _____/min Respiratory rate: _____ /min Body weight: _____ kg / _____ lb

Inspection:

Behavior: _____

Signs of prematurity? __no __yes (__Haircoat __Forehead __Ears __Joints __Tendons _____)

Skin and haircoat: _____

Body condition: _____

Suckle reflex: __good __moderate __weak __none _____

Eyes: __normal __Entropion (L)(R) __Uveitis (L)(R) __Corneal ulcer (L)(R) _____

Cardiovascular

Pulse quality: __strong __moderate __weak / __regular __irregular _____

Mucous membranes: _____ CRT: ___ sec. Skin turgor: _____

Jugular veins: __normal __collapsed __distended _____ Catheter __left __right

Cardiac auscultation: HR: _____ Intensity: _____ Rhythm: __regular __irregular _____

Murmurs: __no __yes _____

Respiration

Nasal discharge: __no __yes _____ Cough: __no __yes _____

Lymph nodes: __normal:_____ Auscultation: __normal: _____

GI tract

Colic: __no __yes _____ GL sounds: _____ Abd. distention: __no __yes _____

Fecal consistency: _____ Digital palpation/Meconium: _____

Urogenital

Umbilicus: __normal _____

Urination: __no __yes __straining _____ Scrotum/Testes – Vulva/Vagina:___normal _____

Musculoskeletal

Joints: __normal _____

Lameness: ___ no __yes _____

Deformations/Angular limb deformities: _____ no __yes _____

Neurologic:

__normal _____

Seizures: __ no __ yes _____

Senior Student: _____ Attending Clinician: _____

Foal Examination Protocol

Fig. 19-4, cont'd

localized disease. Fever is a specific, but not sensitive, sign of sepsis in foals. The presence of petechia in oral, nasal, ocular, or vaginal mucous membranes, the pinna, or coronary bands is considered a specific indicator of sepsis, although this has not been documented by appropriate studies. A similar comment applies for injection of the scleral vessels. A scoring system (the sepsis score) has been developed to aid in the identification of foals with sepsis.

The **sepsis score** was developed with the intention of aiding identification of foals with sepsis, thereby facilitating appropriate treatment. A table for calculation of the sepsis score (the modified sepsis score) is provided in Table 19-11. Foals with a score of 12 or greater are considered to be septic, with a sensitivity of 94% in the original report. However, more recent studies, including one of 1095 foals, have found the sensitivity and specificity of the sepsis score to be less than the original report. The modified sepsis score detected sepsis with a sensitivity of 56% and a specificity of 73% using a cutoff value of 11 or more. A cutoff value of 7 yielded a sensitivity of 84% and specificity of 42%.[3] These recent studies are broadly consistent with earlier studies that demonstrate that the sepsis score has limited sensitivity (67%, 95% CI 59% to 75%) and specificity (76%, 95% CI 68% to 83%) in foals less than 10 days of age. Similarly, 49% of 101 foals with positive blood cultures had a sepsis score of 11 or less, indicating a low specificity of the test. The low to moderate sensitivity of the sepsis score for detection of sepsis or bacteremia means that many foals with sepsis are incorrectly diagnosed as being nonseptic (i.e., a high false-negative rate), whereas a moderate to low specificity means that the false-positive rate might be excessive, with a number of foals being considered septic when they are not. This is an important shortcoming of the test because accurate and prompt identification of foals with sepsis is assumed to be important for both prognostication and selection of treatment. The sepsis score might be useful in some situations, but its shortcomings should be recognized when using it to guide treatment or determine prognosis.

Prematurity and Dysmaturity

Detection of **prematurity** is important because it is a strong risk factor for development of other diseases during the immediate postpartum period. The detection of prematurity is often based on the length of gestation. However, the duration of gestation in Thoroughbred horses varies considerably, with 95% of mares foaling after a gestation of 327 to 357 days. The generally accepted "average" gestation is 349 days, with fillies having shorter gestations than do colts (348 versus 350 days) and gestation length declining by approximately 20 days, from 360 to 340 days, in Standardbred mares in New Zealand.[4] Ponies have a shorter gestation (333 days, range 315 to 350 days). Therefore a diagnosis of prematurity should be based not just on gestational age but also on the results of physical, hematologic, and serum biochemical examination of the newborn. Factors helping in the determination of prematurity are listed in Table 19-4. Foals that are immature (premature) at birth typically have low birth weight and small body size, a short and silky hair coat, and laxity of the

Table 19-4 Criteria to assess stage of maturity of the newborn foal

Criterion	Premature	Full term
Physical		
Gestational age	320 d	Normally > 330 d
Size	Small	Normal or large
Coat	Short and silky	Long
Fetlock	Overextended	Normal extension
Behavior		
First stand	>120 min	<120 min
First stand	>3 h	<3 h
Suck reflex	Poor	Good
Righting reflexes	Poor	Good
Adrenal activity		
Plasma cortisol values over first 2 h postpartum	Low levels (<30 ng/mL)	Increasing levels (120–140 ng/mL) at 30–60 min postpartum
Plasma ACTH values over first 2 h postpartum	Peak values (≈650 pg/mL) at 30 min postpartum and declining subsequently	Declining values from peak (300 pg/mL at birth)
Response to synthetic ACTH1-24 (short-acting Synacthen), dose 0.125 mg IM	Poor response shown by a 28% increase in plasma cortisol and no changes in neutrophil:lymphocyte ratio	Good response shown by a 208% increase in plasma cortisol and widening of neutrophil:lymphocyte ratio
Hematology		
Mean cell volume (fl)	>39	<39
White blood cell count ($\times 10^9$/L)	6.0	8.0
Neutrophil:lymphocyte ratio	<1.0	>2.0
Carbohydrate metabolism		
Plasma glucose levels over first 2 h postpartum	Low levels at birth (2–3 mmol/L), subsequently declining	Higher levels at birth (4.1 mmol/L), maintained
Plasma insulin levels over first 2 h postpartum	Low levels at birth (8.6 µU/mL), declining	Higher levels at birth (16.1 µU/mL), maintained
Glucose tolerance test (0.5 mg/kg body weight IV)	Slight response demonstrated by a 100% increase in plasma insulin at 15 min postadministration	Clear response demonstrated by a 250% increase in plasma insulin at 5 min postadministration
Renin–angiotensin–aldosterone system		
Plasma renin substrate	Higher and/or increasing levels during 15–60 min postpartum	Low (<0.6 µg/mL) and declining levels during 15–30 min postpartum
Acid–base status (pH)	<7.25 and declining	>7.3 and maintaining or rising

IM, intramuscularly; IV, intravenously.

flexor and extensor tendons. The cranium is rounded, and the pinnae lack tone (droopy ears). The foals are typically weak and have trouble standing, which is exacerbated by laxity of the flexor tendons and periarticular ligaments. **Dysmature** (postmature) foals are typically large, although they can be thin, and have a long hair coat and flexure tendon contracture. These signs are consistent with prolonged gestation combined with inadequate intrauterine nutrition. Healthy foals stand approximately 65 min (interquartile range, 45 to 100 minutes) after birth.[4] Examination of the placenta, either by ultrasonographic examination before birth or by direct examination, including histologic and microbiologic testing, after birth is useful in identifying abnormalities that have significance for the newborn.

Hypoxia

Hypoxia during late gestation, birth, or the immediate postpartum period has a variety of clinical manifestations depending on the tissue or organ most affected. Signs of central nervous system dysfunction are often assumed to be a result of cerebral hypoxia during birth, although neonatal maladjustment syndrome does not appear to be related to hypoxia (see "Neonatal Maladjustment Syndrome," page 1871). Other signs suggestive of peripartum hypoxia include colic and anuria.

Hypoglycemia

Foals that are hypoglycemic because of inadequate intake, such as through mismothering, congenital abnormalities, or concurrent illness, are initially weak, with rapid progression to somnolence and coma.

Endocrine Abnormalities

Abnormalities in endocrine function of foals are common and often associated with risk of death.[1,5-10] Septic foals have higher serum ACTH, cortisol, and ACTH:cortisol ratios, and higher serum parathyroid hormone concentrations (but not calcitonin concentrations) than do healthy foals of the same age.[5,6] Septic foals have lower insulin and IGF-1 and higher ghrelin, growth hormone, and glucagon concentrations than do healthy foals.[7,8] Arginine vasopressin concentrations are higher in septic foals.[9] Plasma adrenomedullin concentrations are highest in sick foals (both septic and nonseptic) and might be a useful marker of foal health.[10] Critically ill foals may also have evidence on nonthyroidal illness syndrome (see "Diseases of the Thyroid," Chapter 17).[11]

DIAGNOSTIC IMAGING

Radiographic and ultrasonographic examination of neonates can be useful in determining maturity and the presence of abnormalities. Prematurity is evident as failure or inadequate ossification of cuboidal bones in the carpus and tarsus. Radiographs of the thorax should be obtained if there is any suspicion of sepsis or pneumonia because thoracic auscultation has poor sensitivity in detecting pulmonary disease in newborns. The severity of abnormalities in the lungs of foals detected by radiographic examination is related to prognosis, with foals with more severe disease having a worse prognosis for recovery. Abdominal radiographs may be useful in determining the site of gastrointestinal disease (see discussion of foal colic).

Ultrasonography is a particularly useful tool for examination of neonates, in large part because their small size permits thorough examination of all major body cavities. Ultrasonography of the umbilical structures can identify omphalitis and abscesses of umbilical remnants and, when available, is indicated as part of the physical examination of every sick neonate.

Examination of the **umbilical structures** can reveal evidence of infection, congenital abnormalities, and urachal tears. Examination of the umbilicus can be achieved using a 7.5-mHz linear probe (such as that commonly used for reproductive examination of mares), although sector scanners provide a superior image. Examination of the umbilical structures should include examination of the navel and structures external to the body wall, the body wall, the umbilical stump as it enters the body wall and separates into the two umbilical arteries, the urachus and apex of the bladder, and the umbilical vein. The size and echogenicity of each of these structures should be determined. For foals less than 7 days of age, the intraabdominal umbilical stump should be less than 2.4 cm in diameter, the umbilical vein less than 1 cm, and the umbilical arteries less than 1.4 cm (usually < 1 cm). Examination of these structures should be complete: the umbilical vein should be visualized in the umbilical stump and then followed as it courses along the ventral abdominal wall and into the liver; the umbilical arteries should be visualized in the umbilical stump and then as they separate from that structure and course over the lateral aspects of the bladder; the urachus should be visualized from the external umbilical stump through the body wall and as it enters the bladder.

Abnormalities observed frequently in the umbilical structures include overall swelling, consistent with omphalitis; gas shadows in the urachus or umbilical stump, which are indicative of either a patent urachus allowing entry of air or growth of gas-producing bacteria; and the presence of flocculent fluid in the urachus, vein, or artery, which is consistent with pus. Urachal tears can be observed, especially in foals with uroperitoneum.

Ultrasonographic examination of the **abdomen** is useful in identifying abnormalities of gastrointestinal function and structure, including intestinal distension or thickening of the intestinal wall. Thickness of the wall of the intestinal tract of healthy Standardbred foals of less than 5 days of age are as follows (95% predictive interval): 1.6 to 3.6 mm for the stomach, 1.9 to 3.2 mm for the duodenum, 1.9 to 3.1 mm for the jejunum, 1.3 to 2.2 mm for the colon, and 0.8 to 2.7 mm for the cecum.[12] Intussusceptions are evident as "donut" lesions in the small intestine, but evaluation of the clinical importance of these findings should be considered in the context of the foal. Intussusceptions are detected in a large proportion of healthy neonatal foals as incidental findings.[12] Gastric outflow obstruction should be suspected in foals with a distended stomach evident on ultrasonographic examination of the abdomen. Herniation through the umbilicus or inguinal ring can be confirmed by ultrasonographic examination.[13] Uroperitoneum is readily apparent as excessive accumulation of clear fluid in the abdomen. Hemorrhage into the peritoneum can be detected as accumulation of echogenic, swirling fluid. Accumulation of inflammatory fluid, such as in foals with ischemic intestine, is detected by the presence of flocculent fluid.

Ultrasonographic examination of the **chest** can reveal the presence of pleural abnormalities, consolidation of the lung (provided that the consolidated lung is confluent with the pleura), accumulation of fluid in the pleural space (hemorrhage secondary to birth trauma and fractured ribs, inflammatory fluid in foals with pleuritis), pneumothorax (usually secondary to lung laceration by a fractured rib), or congenital abnormalities of the heart.

Advanced imaging modalities, such as **computed tomography (CT) and magnetic resonance imaging (MRI)**, are available at referral centers and are practical in foals and other neonates because of the small size of the animals. These modalities are useful in detection of intrathoracic and intraabdominal abnormalities, including abscesses, gastrointestinal disease, and congenital abnormalities. MRI is particularly useful for diagnosis of diseases of the brain and spinal cord.

CLINICAL PATHOLOGY

Serum Immunoglobulin Concentration

Serum or plasma immunoglobulins are associated with the risk of death in hospitalized foals. Foals with serum IgG concentration less than or equal to 4.0 g/L were 4.7 (95% CI 2.6 to 8.5) times as likely to die as were foals with a concentration greater than 8 g/L. Foals with an IgG of greater than 4 g/L and less than 8 g/L were 3.7 (2.0 to 6.8) times as likely to die as were foals with concentrations above 8 g/L.[14]

Serum immunoglobulin G (IgG) concentration, or its equivalent, must be measured in every ill or at-risk newborn and should be repeated every 48 to 96 hours in critically ill neonates. A variety of tests are available for

rapid detection of FTPI in foals and calves. Although measurement of serum IgG concentration is ideally performed by the gold standard test, a radial immunodiffusion, this test requires at least 24 hours to run, whereas the stall-side or chemistry analyzer tests can be run in a few minutes. The sensitivity and specificity have been determined for a number of these rapid tests. Overall, most tests have high sensitivity (>80%), meaning that the few foals that have low concentrations of IgG are missed, but poor specificity (50% to 70%), meaning that many foals that have adequate concentrations of immunoglobulin are diagnosed as having inadequate concentrations. The exact sensitivity and specificity depend on the test used and the concentration of immunoglobulin considered adequate. The high sensitivity and low specificity of most of the available rapid tests result in a number of foals that do not need a transfusion receiving one. However, this error is of less importance than that of foals that should receive a transfusion not receiving one.

Serum or plasma concentrations of IgG should be measured after approximately 18 hours of age, and preferably before 48 hours of age—the earlier FTPI is recognized, the better the prognosis for the foal. Foals that ingest colostrum within the first few hours of birth have minimal increases in serum IgG concentration over that achieved at 12 hours of age, suggesting that measurement of serum IgG concentration as early as 12 to 18 hours after birth is appropriate. This early measurement of serum IgG concentration could be especially important in high-risk foals. The oldest age at which measurement of serum IgG is useful in foals is uncertain, but depends on the clinical condition of the foal. Typically, immunoglobulin concentrations of foals that have adequate concentrations of IgG within the first 24 hours reach a nadir at about 6 weeks of age and then rise to concentrations similar to adults over the next 2 to 3 months.

Hematology

It is important to recognize that the hemogram of neonates differs from that of older animals (Table 19-5) because these differences can affect the clinical assessment of the animal. The hematologic and serum biochemical values of foals and calves can vary markedly during the first days and weeks of life, and it is important that these maturational changes are taken into account when assessing results of hematologic or serum biochemical examination of foals. Hematologic examination can reveal evidence of hemolytic disease, bacterial or viral infection, or prematurity/dysmaturity (Table 19-4). Repeated hemograms are often necessary to monitor for development of sepsis and responses to treatment.

Foals with **sepsis** can have a leukocyte count in the blood that is low, within the reference range, or high. Approximately 40% of foals with sepsis have blood leukocyte counts that are below the reference range. Most foals with sepsis (approximately 70%) have segmented neutrophil counts that are below the reference range, with fewer than 15% of foals having elevated blood neutrophil counts. Concentrations of band cells in blood are above the reference range in almost all foals with sepsis. Some foals born of mares with placentitis have a very pronounced mature neutrophilia without other signs of sepsis; these foals typically have a good prognosis. Lymphopenia is present in foals with equine herpervirus-1 septicemia or Arabian foals with severe

Table 19-5 Hematologic values of normal foals and calves

	FOALS			CALVES		
Variable	*<12 h*	*1 week*	*1 month*	*24 h*	*48 h*	*3–4 weeks*
PCV (%)	42.5 ± 3.4	35.3 ± 3.3	33.9 ± 3.5	34 ± 6	32 ± 6	35 ± 3
(L/L)	0.43 ± 0.03	0.35 ± 0.03	0.33 ± 0.04	0.34 ± 0.06	0.32 ± 0.06	0.35 ± 0.03
Plasma protein (g/dL)	6.0 ± 0.8	6.4 ± 0.6	6.1 ± 0.5	6.4 ± 0.7	6.4 ± 0.7	6.4 ± 0.3
(g/L)	60 ± 8	64 ± 6	61 ± 5	64 ± 7	64 ± 7	64 ± 3
Fibrinogen (mg/dL)	216 ± 70	290 ± 70	400 ± 130	290 ± 105	335 ± 120	285 ± 145
(g/L)	2.16 ± 0.7	2.90 ± 0.7	4.00 ± 1.30	2.90 ± 1.05	3.35 ± 1.20	2.85 ± 1.45
Hemoglobin (g/dL)	15.4 ± 1.2	13.3 ± 1.2	12.5 ± 1.2	10.9 ± 2.1	10.5 ± 1.8	11.3 ± 1.02
(g/L)	154 ± 12	130 ± 12	125 ± 12	109 ± 21	105 ± 18	113 ± 10
Red blood cells ($\times 10^6/\mu L$)	10.7 ± 0.8	8.8 ± 0.6	9.3 ± 0.8	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
($10^{12}/L$)	10.7 ± 0.8	8.8 ± 0.6	9.3 ± 0.8	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
MCV (fL)	40 ± 2	39 ± 2	36 ± 1	41 ± 3	41 ± 3	39 ± 2
MCHC (g/dL)	36 ± 2	38 ± 1	37 ± 1	32.1 ± 0.8	32.6 ± 1.0	32.8 ± 1.6
(g/L)	360 ± 20	380 ± 10	370 ± 10	320 ± 8	326 ± 10	328 ± 16
MCH (pg)	14 ± 1	15 ± 1	14 ± 1			
Nucleated cells ($10^6/\mu L$)	9500 ± 2500	9860 ± 1800	8150 ± 2030	9810 ± 2800	7760 ± 1950	8650 ± 1690
($10^9/L$)	9.5 ± 2.5	9.86 ± 1.80	8.15 ± 2.03	9.81 ± 2.80	7.76 ± 1.95	8.65 ± 1.69
Neutrophils ($10^6/\mu L$)	7950 ± 2200	7450 ± 1550	5300 ± 200	6500 ± 2660	4110 ± 2040	2920 ± 1140
($10^9/L$)	7.95 ± 2.20	7.45 ± 1.55	5.30 ± 0.20	6.50 ± 2.66	4.11 ± 2.04	2.92 ± 1.14
Band neutrophils ($10^6/\mu L$)	24 ± 40	0	4 ± 13	310 ± 460	210 ± 450	10 ± 30
($10^9/L$)	0.02 ± 0.04	0	0.00 ± 0.01	0.31 ± 0.46	0.21 ± 0.45	0.01 ± 0.03
Lymphocytes ($10^6/\mu L$)	1350 ± 600	2100 ± 630	2460 ± 450	2730 ± 820	2850 ± 880	5050 ± 800
($10^9/L$)	1.35 ± 0.6	2.10 ± 0.63	2.46 ± 0.45	2.73 ± 0.82	2.85 ± 0.88	5.05 ± 0.80
Thrombocytes ($10^3/\mu L$)	266 ± 103	250 ± 70	300 ± 80			
($10^9/L$)	266 ± 103	250 ± 70	300 ± 80			
Serum Fe (µg/dL)	380 ± 60	175 ± 80	138 ± 60		71 ± 60	127 ± 60
(mg/L)	3.80 ± 0.6	1.75 ± 0.8	1.38 ± 0.6		0.7 ± 0.6	1.27 ± 0.6
TIBC (µg/dL)	440 ± 50	385 ± 80	565 ± 65		420 ± 67	
(mg/L)	4.40 ± 0.5	3.85 ± 0.8	5.65 ± 0.65		4.2 ± 0.7	
UIBC (µg/dL)	55 ± 40	210 ± 100	430 ± 85			
(mg/L)	0.55 ± 0.4	2.10 ± 1.00	4.30 ± 0.85			
Iron saturation (%)	87 ± 9	46 ± 20	25 ± 12			

Sources: Harvey JW et al. Equine Vet J *1984; 16:347; Adams R et al.* Am J Vet Res *1992; 53:944; Tennant B et al.* Cornell Vet *1975; 65:543.*

combined immunodeficiency. Thrombocytopenia occurs in some foals with sepsis. Hyperfibrinogenemia is common in foals that have sepsis, although the concentration might not be above the reference range in foals examined early in the disease.

Hyperfibrinogenemia is common in foals born of mares with placentitis and reflects systemic activation of the inflammatory cascade even in foals that have no other evidence of sepsis. Serum amyloid A concentrations are above 100 mg/L in foals with sepsis. Septic foals also have blood concentrations of proinflammatory cytokines, and of plasma C-reactive protein,[15] that are higher than those in healthy foals. Plasma haptoglobin concentrations are not different between surviving and nonsurviving foals and are only minimally lower in foals with sepsis than in nonseptic hospitalized foals.[15] Indices of coagulation are prolonged in foals with sepsis, and concentrations of antithrombin and protein C antigen in plasma are lower than in healthy foals. These abnormalities indicate that coagulopathies are common in septic foals.

Prematurity is associated with a low neutrophil:lymphocyte ratio (<1.5:1) in blood and red cell macrocytosis (Table 19-4). A neutrophil:lymphocyte ratio above 2:1 is considered normal. Premature foals that are not septic can have low blood neutrophil counts but rarely have immature neutrophils (band cells) or toxic changes in neutrophils.

Serum Biochemistry

Care should be taken in the interpretation of the results of serum biochemical examinations because normal values for newborns are often markedly different from those of adults, and they can change rapidly during the first days to weeks of life (Table 19-6). Serum biochemical examination can reveal electrolyte abnormalities associated with renal failure, diarrhea, and sepsis. Elevations in serum bilirubin concentration or serum enzyme activities may be detected. As a minimum, blood glucose concentrations should be estimated using a chemical strip in depressed or recumbent newborns.

Markedly elevated serum **creatinine** concentrations are not uncommonly observed in foals with no other evidence of renal disease. The elevated serum creatinine in these cases is a consequence of impaired placental function during late gestation, with the consequent accumulation of creatinine (and probably other compounds). In foals with normal renal function, which most have, the serum creatinine concentration should decrease to 50% of the initial high value within 24 hours. Other causes of high serum creatinine concentration that should be ruled out are renal failure (dysplasia, hypoxic renal failure) and postrenal azotemia (uroperitoneum).

Blood or plasma **l-lactate concentrations** are useful indicators of the presence and severity of systemic disease that impairs oxygen delivery to tissue (hypoxemia, poor perfusion, anemia) or use by tissue (endotoxemia), but it is not specific for any one disease or group of diseases, with the exception that septic foals have higher concentrations than do nonseptic foals.[16-19] However, the difference between septic and nonseptic foals (4.8 [range, 0.6 to 37) and 3.3 [range, 0.3 to 21] mmol/L) is not sufficiently different to make it useful in an individual animal.[20] Blood lactate concentrations of healthy foals are greatest at birth to 12 hours of age and then decline.[16] Blood lactate concentrations of foals that do not survive their acute illness do not decline in response to therapy,[16] and risk of death increases by 1.1 for each mmol/L increase in blood lactate concentration of foals at time of admission to a veterinary hospital.[17,20] Serial measurement of blood lactate concentrations and calculation of an "area-under-the-curve" measure also provides useful information related to risk of death, but not the cause of the disease.

Sepsis is usually associated with hypoglycemia, although septic foals can have normal or elevated blood glucose concentrations. Hypoglycemia is attributable to failure

Table 19-6 Serum biochemical values of normal foals and calves

	FOALS			CALVES		
Variable	*<12 h*	*1 week*	*1 month*	*24 h*	*48 h*	*3 weeks*
Na^+ (mEq/L) (mmol/L)	148 ± 8	142 ± 6	145 ± 4	145 ± 7.6	149 ± 8.0	140 ± 6
K^+ (mEq/L) (mmol/L)	4.4 ± 0.5	4.8 ± 0.5	4.6 ± 0.4	5.0 ± 0.6	5.0 ± 0.6	4.9 ± 0.6
Cl (mEq/L) (mmol/L)	106 ± 6	102 ± 4	103 ± 3	100 ± 4	101 ± 5.0	99 ± 4
Ca^{2+} (mg/dL)	12.8 ± 1	12.5 ± 0.6	12.2 ± 0.6	12.3 ± 0.2	12.3 ± 0.3	9.4 ± 0.6
(mmol/L)	3.2 ± 0.25	3.1 ± 0.15	3.05 ± 0.15	3.1 ± 0.1	3.1± 0.1	2.3 ± 0.2
PO_4^- (mg/dL)	4.7 ± 0.8	7.4 ± 1.0	7.1 ± 1.1	6.9 ± 0.3	7.6 ± 0.2	7.1 ± 6.4
(mmol/L)	1.52 ± 0.26	2.39 ± 0.32	2.29 ± 0.36	2.3 ± 0.1	2.5 ± 0.1	2.3 ± 1.8
Total protein (g/dL)	5.8 ± 1.1	6.0 ± 0.7	5.8 ± 0.5	5.6 ± 0.5	6.0 ± 0.7	6.5 ± 0.5
(g/L)	58 ± 11	60 ± 7	58 ± 5	56 ± 5	60 ± 7	65 ± 5
Albumin (g/dL)	3.2 ± 0.3	2.9 ± 0.2	3.0 ± 0.2			
(g/L)	32 ± 3	29 ± 2	30 ± 2			
Creatinine (mg/dL)	2.5 ± 0.6	1.3 ± 0.2	1.5 ± 0.2			
(µmol/L)	221 ± 53	115 ± 18	133 ± 18			
Urea nitrogen (mg/dL)	19.7 ± 4.4	7.8 ± 3.4	9.0 ± 3.0	12.6 (7.1–21.2)		
(mmol/L)	3.4 ± 1.6	1.6 ± 0.6	1.7 ± 0.5	2 (1.5–3.6)		
Glucose (mg/dL)	144 ± 30	162 ± 19	162 ± 22	130 ± 27	114 ± 19	70 (52–84)
(mmol/L)	8.0 ± 1.6	9.0 ± 1.0	9.0 ± 1.2	7.23 ± 1.5	6.34 ± 1.1	3.9 (2.9–4.7)
Total bilirubin (mg/dL)	2.6 ± 1.0	1.5 ± 0.4	0.7 ± 0.2	<2.5	<0.9	<0.6
(µmol/L)	45 ± 17	26 ± 6	12 ± 4	<42	<15	<10
Direct bilirubin (mg/dL)	0.9 ± 0.1	0.5 ± 0.2	0.3 ± 0.2	<0.6	<0.3	<0.3
(µmol/L)	15 ± 2	8.5 ± 3	5 ± 3	<10	<5	<5
GGT (IU/L)	47.5 ± 21.5	49.1 ± 21.2		890 ± 200	600 ± 180	70 ± 10
ALK (IU/L)	3040 ± 800	1270 ± 310	740 ± 240	<1150	<1000	<770
AST (IU/L)	199 ± 57	330 ± 85	340 ± 55	<60	<33	<32

Values are mean ± standard deviation.
ALK, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gammaglutamyl transpeptidase.
Sources: Bauer JE et al. Equine Vet J *1984; 16:361; Pearson EG et al.* J Am Vet Med Assoc *1995; 207:1466; Jenkins SJ et al.* Cornell Vet *1982; 72:403; Dalton RG.* Br Vet J *1967; 123:48; Wise GH et al.* J Dairy Sci *1947; 30:983; Diesch TJ et al.* New Zeal Vet J *2004; 52:256; Patterson WH, Brown CM.* Am J Vet Rev *1986; 47:2461; Thompson JC, Pauli JV.* New Zeal Vet J *1981; 29:223*

to nurse, whereas hyperglycemia indicates loss of normal sensitivity to insulin. Indicators of renal, hepatic, or cardiac (troponin) damage can increase in foals with sepsis, causing organ damage or failure. Foals with sepsis tend to have elevated concentrations of cortisol in serum.

Prematurity is associated with low concentrations of cortisol in plasma or serum and minimal increase in response to intramuscular administration of 0.125 mg of exogenous ACTH (corticotropin). Plasma cortisol concentration of normal full-term foals during the first 24 hours of life increases from a baseline value of approximately 40 ng/mL to over 100 ng/mL 60 minutes after ACTH administration, whereas plasma cortisol concentrations in premature foals do not increase from values of slightly less than 40 ng/mL. At 2 and 3 days of age, plasma cortisol concentrations of full-term foals increase twofold after ACTH administration, albeit from a lower resting value, but do not increase in premature foals. Blood glucose concentrations of premature foals are often low, probably because of inability to nurse.

Blood Gas

Arterial blood pH, P_{CO_2}, and P_{O_2} should be measured to determine the newborn's acid–base status and the adequacy of respiratory function. Foals with hypoxemia are five times more likely to have pulmonary radiographic abnormalities. Prolonged lateral recumbency of foals compromises respiratory function, and arterial blood samples should be collected with the foal in sternal recumbency. Repeated sampling may be necessary to detect changes in respiratory function and to monitor the adequacy of oxygen supplementation or assisted ventilation.

Blood Culture

Identification of causative organisms of sepsis in foals can aid in prognostication and potentially in selection of therapy, although there does not appear to be a relation between antimicrobial sensitivity of organisms isolated from blood, as determined by Kirby–Bauer testing, and survival of foals. Anaerobic and aerobic blood cultures should be performed as early in the disease process as possible, and preferably before initiation of antibiotic treatment, although antimicrobials should not be withheld from a newborn with confirmed or suspected sepsis to obtain a result from blood culture. Strict aseptic technique should be used when collecting blood for culture. Blood cultures should also be collected if there is a sudden deterioration in the newborn's condition.

Gram-negative enteric bacteria are the most common isolates from blood of newborn foals, with *E. coli* the most common isolate. *A. equuli* is also a common isolate from foals. There are important differences in diseases produced by the various organisms, with foals with *A. equuli* septicemia being twice as likely to die, seven times more likely to have been sick since birth, six times more likely to have diarrhea, five times more likely to have a sepsis score of more than 11, and three times more likely to have pneumonia than foals with sepsis associated with other bacteria.

A problem with blood culture is the time needed to obtain either interim or final results because this can delay detection of infection or decisions to use focused antimicrobial therapy. Use of real-time polymerase chain reaction (PCR) to detect bloodstream infection of foals will likely supplement conventional blood culture in foals.[21]

Other Body Fluids

Synovial fluid should be submitted for aerobic and anaerobic culture, Gram stain, and cytologic examination when signs of synovitis, such as lameness, joint effusion, or joint pain, are present.

Analysis of cerebrospinal fluid (CSF) is indicated in newborns with signs of neurologic disease. Samples of CSF should be submitted for cytologic examination, measurement of total protein concentration, Gram stain, and bacterial culture.

Urinalysis may provide evidence of renal failure (casts) or urinary tract infection (white blood cells).

Abdominal fluid should be collected in foals with abdominal pain or distension and should be submitted for cytologic examination and, if uroperitoneum is suspected, measurement of creatinine concentration.

TREATMENT

The principles of care of the critically ill newborn farm animal are as follows:

- The newborn should be kept in a sanitary environment to minimize the risk of nosocomial infections.
- Systemic supportive care should be provided to maintain homeostasis until the newborn is capable of separate and independent existence.
- There should be frequent and comprehensive reevaluations of all body systems to detect signs of deterioration and allow early correction.
- Provision should be made to ensure adequate passive immunity (serum or plasma IgG concentration > 8 g/L) to reduce the risk of secondary infections or to treat existing infections. Transfer of passive immunity should be evaluated using laboratory methods that measure serum or plasma IgG concentration.

The level of care provided depends on the value of the animal and the available facilities, personnel, and expertise. Newborns of limited financial worth are usually treated on the farm, whereas valuable foals and calves can be referred for specialist care. Referral of sick neonates to institutions and practices with expertise in provision of critical care to newborns should be timely and prompt and, when necessary, should be recommended on the first visit.

Nursing Care

The sophistication of care for critically ill newborns depends on the facilities and personnel available, with intensive management requiring dedicated facilities and trained personnel available 24 hours a day. The minimum requirement for providing basic care of ill newborns is a sanitary area in which the newborns can be protected from environmental stress. Often this means separating the newborn from its dam.

Excellent nursing care is essential for maximizing the likelihood of a good outcome. Critically ill animals might benefit from constant nursing care. Strict attention must be paid to maintaining the sanitary environment to minimize the risk of nosocomial infections. The newborn should be kept clean and dry and at an ambient temperature in its thermoneutral zone. Bedding should prevent development of decubital ulcers. Foals should be maintained in sternal recumbency, or at least turned every 2 hours, to optimize their respiratory function.

Correction of Failure of Transfer of Passive Immunity

Colostral Immunoglobulin

Ideally, adequate transfer of passive immunity is achieved by the newborn nursing its dam and ingesting an adequate amount of colostrum containing optimal concentrations of immunoglobulins, principally IgG (IgGb) in foals. Foals need approximately 2 g of IgG per kilogram of body weight to achieve a plasma concentration of 2000 mg/dL (20g/L); therefore a 45-kg foal needs approximately 90 g of IgG to attain a normal serum IgG concentration (or approximately 40 g to achieve a serum IgG concentration of 800 mg/dL [8 g/L]). Assuming that colostrum contains on average 10,000 mg/dL (100 g/L), foals must ingest at least 1 L of colostrum to obtain sufficient immunoglobulin. Because colostral IgG concentration varies considerably (from 2000 to 30,000 mg/dL), specific recommendations regarding the quantity of colostrum to be fed to neonatal foals cannot be made with certainty. However, colostrum with a specific gravity of more than 1.060 has an IgG concentration of more than 3000 mg/dL (30 g/L), suggesting that foals should ingest at least 1.5 L to achieve serum IgG concentrations above 800 mg/dL (8 g/L).

Critical Plasma IgG Concentrations in Foals

There is some debate as to what constitutes a critical serum or plasma IgG concentration. Foals that ingest an adequate amount of colostrum typically have serum immunoglobulin concentrations during the first week of life greater than approximately 2000 mg/dL (20 g/L). Both 400 mg/dL

(4 g/L) and 800 mg/dL (8 g/L) have been recommended as concentrations below which foals should be considered to have increased likelihood of contracting infectious disease, but recent evidence strongly supports the use of 800 mg/dL (8 g/L) as the minimal concentration in hospitalized foals. However, on a well-managed farm the serum IgG concentration was not predictive of morbidity or mortality among foals, suggesting that serum immunoglobulin concentration in some populations of foals is not an important risk factor for infectious disease. The foals in this study were from an exceptionally well-managed farm. Other researchers have found that foals with serum IgG concentration below 800 mg/dL (8 g/L) are at markedly increased risk of subsequent development of infectious disease, including sepsis, pneumonia, and septic arthritis. It is likely that there is no single concentration of IgG in serum that is protective in all situations, and the concentration of IgG in serum that is desirable in an individual foal depends on the risk factors for infectious disease of that foal. Our opinion is that a minimum serum IgG in foals free of disease and housed in closed bands on well-managed farms is 400 mg/dL (4 g/L). For foals at increased risk of disease—for instance, those on large farms with frequent introduction of animals and foals that are transported or housed with foals with infectious disease—the minimum advisable serum IgG concentration is 800 mg/dL (8 g/L). Foals that have infectious disease should have serum IgG concentrations of at least 800 mg/dL, and it might be advantageous for these foals to have even higher values, as indicated by the enhanced survival of foals with septic disease administered equine plasma regardless of their serum IgG concentration. This therapeutic advantage could be because of the additional IgG or because of other factors included in the plasma. Transfusion of plasma to sick foals improves neutrophil function, an important advantage given that oxidative burst activity of neutrophils from septic foals is reduced compared with that in healthy foals.

Plasma Transfusion

The ability of foals to absorb macromolecules, including immunoglobulins, declines rapidly after birth, being 22% of that at birth by 3 hours of age and 1% of that at birth by 24 hours of age. Consequently, by the time that FTPI is recognized, it is no longer feasible to increase serum IgG concentrations by feeding colostrum or oral serum products. Foals should then be administered plasma or serum intravenously. The **amount of plasma** or serum to be administered depends on the target value for serum IgG concentration and the initial serum IgG concentration in the foal. For each gram of IgG administered per kilogram of body weight of the foal, serum IgG concentration increases by approximately 8.7 mg/dL (0.87 g/L) in healthy foals and 6.2 mg/dL (0.62 g/L) in sick foals. To achieve serum IgG concentrations above 800 mg/dL (8 g/L) in foals with serum IgG concentrations below 400 mg/dL (4 g/L), they should be administered 40 mL/kg of plasma containing at least 20 g/L of IgG. Similarly, foals with serum IgG concentrations above 400 mg/dL (4g/L) but below 800 mg/dL (8 g/L) should be administered 20 mL/kg of plasma. For 45-kg foals, these recommendations translate to administration of 1 or 2 L of plasma, respectively.

The ideal product for transfusion into foals with FTPI is **fresh frozen plasma** harvested from horses that are Aa and Qa antigen-negative and that do not have antibodies against either or both of these red blood cell antigens (see the discussion of neonatal isoerythrolysis). The donor horses should have been vaccinated against the common diseases of horses and have tested negative for equine infectious anemia. Good-quality commercial products specify the minimum concentration of IgG in the plasma. Concentrated serum products that do not need to be frozen until use are available. These are much more convenient for field use than are plasma products that must be frozen until immediately before transfusion. However, the IgG concentration of these products is often not specified, and the manufacturer's recommendations for dosing often result in administration of inadequate amounts of immunoglobulin. Serum products can produce adequate concentrations of IgG in foals, but the dose is usually two to three times that recommended by the manufacturer. An adequate dose of concentrated serum products is approximately 1 L for some products. The crucial point is that it is not the volume of plasma or serum that is administered that is important, but rather the quantity of immunoglobulin delivered to the foal. A total of 20 to 25 g of IgG is required to raise the serum IgG concentration of a 50-kg foal by 400 mg/dL (4 g/L).

Plasma should be administered intravenously; oral administration is likely to be wasteful, especially in foals more than a few hours old. Frozen plasma should be thawed at room temperature or by immersion in warm (<37° C, 100° F) water. Thawing by immersion in water at temperatures higher than body temperature can cause denaturation and coagulation of proteins, with loss of efficacy of transfused immunoglobulins. Plasma should never be thawed or warmed using a microwave because this denatures the proteins.

Administration of plasma should be intravenous; intraperitoneal administration, such as used in pigs or small ruminants, has not been investigated in foals. The thawed plasma should be administered through a jugular catheter using a blood administration set containing a filter (160- to 270-µm mesh) to prevent infusion of particulate material. Strict asepsis should be used. The foal should be adequately restrained for the procedure, with some active foals needing moderate tranquillization. Premedication with antihistamines or nonsteroidal antiinflammatory drugs is usually not necessary. The plasma should be infused slowly at first, with the first 20 to 40 mL administered over 10 minutes. During this period the foal should be carefully observed for signs of transfusion reaction, which is usually evident as restlessness, tachycardia, tachypnea, respiratory distress, sweating, or urticaria. If these signs are observed, the transfusion should be stopped, and the foal should be reevaluated and treated if necessary. If no transfusion reactions are noted during the first 10 minutes, the infusion can then be delivered at 0.25 to 1.0 mL/kg/min (i.e., about 1 L/h for a 50-kg foal). Rapid infusion can result in acute excessive plasma volume expansion, with the potential for cardiovascular and respiratory distress.

Serum IgG concentration should be measured after the infusion to ensure that an adequate concentration of IgG has been achieved. Serum IgG can be measured as early as 20 minutes after the end of the transfusion.

Nutritional Support

Provision of adequate nutrition is essential to the recovery of ill newborns. Healthy newborn foals have estimated energy requirements of 500 to 625 kJ/kg/d (120 to 150 kcal/kg/d) and consume approximately 20% of their body weight as milk per day. Measurements of foal energy expenditure using indirect calorimetry reveal expenditure of ~60 to 80 kcal/kg/d in healthy foals, which is reduced to ~50 kcal/kg/d for critically ill foals.[22]

The best food for newborns is the dam's milk, and newborns that are able to do so should be encouraged to nurse the dam. However, if the foal is unable to nurse or the dam is not available, then good-quality milk substitutes should be used. Soy and other plant-protein-based milk replacers are not suitable for newborns. Commercial products formulated for foals, calves, and lambs are available. Human enteral nutrition products supplying 0.7 to 1 kcal/mL (2.8 to 4.1 kJ/mL) can also be used for short-term (several days to a week) support of foals.

It is preferable to provide enteral, rather than parenteral, nutrition to ill newborns with normal or relatively normal gastrointestinal function. Sick neonatal foals should initially be fed 10% of their body weight as mare's milk, or a suitable replacer, every 24 hours, divided into hourly or 2-hour feedings. If the foal does not develop diarrhea or abdominal distension, then the amount fed can be increased over a 24- to 48-hour period to 20% to 25% of the foal's body weight (or 150 kcal/kg/day; 620 kJ/kg/day). Newborns can be fed by nursing a

bottle or bucket or via an indwelling nasogastric tube such as a foal feeding tube, stallion catheter, human feeding tube, or enema tube. Every attempt should be made to encourage the newborn to nurse its dam as soon as the newborn can stand. Adequacy of nutrition can be monitored by measuring blood glucose concentrations and body weight.

Parenteral nutrition (PN) can be provided to newborns that are unable to be fed by the enteral route. This can be achieved by administration of various combinations of solutions containing glucose (dextrose), amino acids, and fat. A commercial product that does not include lipid has been used successfully for up to 12 days in foals. One product that has been used successfully for foals is a solution of amino acids (5%), dextrose (25%), and electrolytes (Clinimix E; Baxter Healthcare Corporation, Deerfield, IL). Lipid emulsion is not added to the preparation. Additional multivitamin supplements including calcium gluconate (provided 2.5 mmol/L), magnesium sulfate (6 mEq/L), B-vitamin complex (thiamine 12.5 mg/L; riboflavin 2 mg/L; niacin 12.5 mg/L; pantothenic acid 5 mg/L; pyridoxine 5 mg/L; cyanocobalamin 5 µg/L), and trace elements (zinc 2 mg/L; copper 0.8 mg/L; manganese 0.2 mg/L; chromium 8 µg/L) are added. Administration is through a catheter, a single-lumen 14-gauge over-the-wire catheter (Milacath), inserted in the jugular vein with its tip placed in the cranial vena cava. A double-T extension set is used to allow concurrent constant-rate infusion of isotonic crystalloid fluids and intravenous administration of medication in one line and PN solution in the other. An infusion pump is used for continuous-rate infusion of the solutions. The PN solution should be prepared under aseptic conditions just before administration and used for only a period of 24 hours after preparation. A 0.22-µm filter is included in the administration line to remove all bacteria, glass, rubber, cellulose fibers, and other extraneous material in the PN solution. The filters and administration sets are changed with each new bag of PN solution.

The rate of PN infusion is determined based on the weight and physical and metabolic condition of the foal. The general protocol is based on the assumption that sick foals expend approximately 50 kcal/kg body weight per day (basal rate).[22] The PN is started at half the basal rate for 12 hours, increasing to the basal rate over 24 to 48 hours, and then in some foals increased slowly to 75 kcal/kg/d if tolerated by the foal. The clinical condition of the foal is assessed frequently. Blood glucose concentrations should be measured every 6 to 8 hours during the introduction and weaning of PN until the blood glucose concentration is stabilized. Insulin can be administered during hyperglycemic crises (≫250 mg/dL) at a dose of 0.1 to 0.4 U/kg regular insulin intramuscularly, but this is rarely needed. When a constant rate of PN is achieved, glucose concentrations should be measured every 8 to 12 hours, depending on the clinical condition of the foal. Foals are weaned off the PN as their clinical condition improves, and enteral feeding is gradually increased. The rate of PN is halved every 4 to 12 hours if blood glucose concentration is stable until half the basal rate is obtained, at which time the infusion is discontinued if the foal is bright, alert, and nursing well.

PN is supplemented with isotonic fluid therapy administered intravenously. The fluid rate and composition are determined based on clinical condition, packed cell volume, total protein, and serum electrolyte concentrations (Na, Cl, Ca, K and HCO_3). The composition and rate are adjusted to maintain normal hydration and electrolyte and acid–base status. During the period that foals receive PN, enteral feeding is initially withdrawn, and the foals are muzzled or separated from the mare. Beginning 24 hours after the institution of PN, 20 to 40 mL of mare's milk ("trophic" feeding) is administered enterally every 4 hours. The trophic feeding provides nutrition to enterocytes and stimulates production of lactase in the small intestine in preparation for resumption of enteral feeding. As the foals are weaned off the PN, enteral feedings are gradually increased from small trophic feeding every 4 hours to allowing the foal to nurse from the mare for 2 to 5 minutes every 2 hours and eventually unrestricted nursing from the mare.

Antimicrobial Treatment

Normal newborns are at risk of acquiring life-threatening bacterial infections, and the risk increases when they do not ingest adequate colostrum in a timely fashion or are subjected to environmental stresses (see the discussion on neonatal infection). Newborns in which bacterial infection is suspected and those at high risk of developing an infection, such as sick newborns with FTPI, should be administered antimicrobials. Antimicrobial therapy should not be delayed pending the results of bacterial culture and antimicrobial sensitivity testing.

The choice of antimicrobial is determined by the likely infecting agent and clinical experience with antimicrobial susceptibility of local strains of pathogens. In general, broad-spectrum antimicrobials are chosen because it is almost impossible to predict, based on clinical signs, the nature of the infecting agent and its antimicrobial susceptibility. Although *Streptococcus* spp. were historically reported to be the cause of most infections in neonatal foals, currently infections of neonatal foals are usually a result of gram-negative organisms, including *E. coli*, *Klebsiella* spp., and *Salmonella* spp. Because of the wide variety of infecting agents and their varying antimicrobial susceptibility, it is possible to make only general recommendations for antimicrobial therapy of neonates. A frequently used antimicrobial regimen is an aminoglycoside (gentamicin or, more commonly, amikacin) and penicillin. Some commonly used drugs and their doses are listed in Table 19-7. Dosage of antimicrobials in foals differs somewhat from that of adults, and the pharmacokinetics of drugs in normal foals are often different from those of the same drug in sick foals. Consequently, higher dosages administered at prolonged intervals are often indicated in sick foals, especially when concentration-dependent drugs such as the aminoglycosides are used.

The response to antimicrobial therapy should be monitored, using physical examination and clinical pathology data, on at least a daily basis. Failure to improve should prompt a reconsideration of the therapy within 48 to 72 hours, and a worsening of the newborn's condition may necessitate changing the antimicrobial sooner than that. The decision to change antimicrobial therapy should be guided, but not determined, by the results of antimicrobial sensitivity testing of isolates from the affected newborn. These antimicrobial susceptibility patterns should be determined locally because the results can vary geographically, although results of studies are published.[23,24] The utility of antimicrobial sensitivity testing in determining optimal antimicrobial therapy for foals has not been determined, although it is likely that, as with mastitis in cows, sensitivity to antimicrobials determined by the Kirby–Bauer method will not be useful in predicting efficacy.

Fluid Therapy

Fluid therapy of newborns differs from that of adult animals because of important differences in fluid and electrolyte metabolism in newborns. The following guidelines are suggested:

- **Septic shock**—sequential boluses of 20 mL/kg delivered over 5 to 20 minutes with reevaluation after each bolus. Usually, 60 to 80 mL/kg is the maximum dose before use of pharmacologic support of blood pressure is considered. Care should be taken to avoid fluid overload, and the foal should be reevaluated after each bolus and the need for continued fluid therapy determined. Continuous infusion of fluid is not indicated.
- **Maintenance support**—this should be determined based on the ongoing losses and the clinical status of the animal. However, general recommendations are as follows:
  - First 10 kg of body weight—100 mL/kg/d
  - Second 10 kg of body weight—50 mL/kg/d

Table 19-7 Antimicrobials used in neonatal foals

Antimicrobial	Dose and route	Frequency	Comments
Amikacin sulfate	25 mg/kg, IM or IV	24 h	Excellent Gram-negative activity, potentially nephrotoxic. Use with a penicillin.
Amoxicillin trihydrate	25 mg/kg, PO	6–8 h	Variable absorption decreasing with age. Limited Gram negative spectrum.
Amoxicillin–clavulanate	15–25 mg/kg, IV	6–8 h	Enhanced Gram-negative spectrum.
Amoxicillin sodium	15–30 mg/kg, IV or IM	6–8 h	Limited Gram-negative spectrum. Use with an aminoglycoside. Safe.
Ampicillin sodium	10–20 mg/kg, IV or IM	6–8 h	Limited Gram-negative spectrum. Use with an aminoglycoside. Safe.
Ampicillin trihydrate	20 mg/kg, PO	6–8 h	Limited Gram-negative spectrum. Variable absorption decreasing with age.
Cefotaxime sodium	15–25 mg/kg, IV	6–8 h	Use for bacterial meningitis. Expensive.
Cefoperazone sodium	20–30 mg/kg, IV	6–8 h	Use for *Pseudomonas* spp. infections.
Cefpodoxime proxetil	10 mg/kg PO	8–12 h	Broad spectrum and well absorbed by foals after oral administration.
Ceftazidime sodium	20–50 mg/kg, IV	6–8 h	Third-generation cephalosporin. Save for refractory infections.
Ceftiofur sodium	10 mg/kg, IV over 15 min	6 h	Broad spectrum. Note higher dose than used in adults.
Chloramphenicol palmitate	50 mg/kg, PO	6–8 h	Broad spectrum, bacteriostatic. Human health risk. Restricted use.
Chloramphenicol sodium succinate	50 mg/kg, IV	6–8 h	Broad spectrum, bacteriostatic. Human health risk. Restricted use.
Ciprofloxacin	5 mg/kg, IV	12 h	Broad spectrum. Potentially toxic to developing cartilage.
Enrofloxacin	5–7.5 mg/kg, PO or IV	12–24 h	Broad spectrum. Potentially toxic to developing cartilage.
Gentamicin sulfate	12 mg/kg, IV or IM	36 h	Good Gram-negative spectrum. Nephrotoxic. Use with a penicillin. Dose should be decreased to 6.6 mg/kg IV or IM every 24 hours for foals > 2 weeks of age.
Metronidazole	15–25 mg/kg, IV or PO	8–12 h	Active against obligate anaerobes and protozoa only.
Oxytetracycline	5 mg/kg, IV	12 h	Variable Gram-negative activity. Safe. Cheap. High and prolonged dose protocols have the potential to result in discoloration of the teeth.
Procaine penicillin G	20,000–40,000 IU/kg, IM	12 h	Very limited Gram-negative activity. Muscle soreness. Cheap.
Sodium or potassium penicillin G	20,000–40,000 IU/kg, IV or IM	6 h	Limited Gram-negative activity. Use with an aminoglycoside.
Pivampicillin	15–30 mg/kg, IV or IM	8 h	Ampicillin prodrug.
Ticarcillin sodium	50 mg/kg, IV	6 h	Active against Gram-negative organisms. Expensive.
Ticarcillin-clavulanate	50 mg ticarcillin/kg, IV	6 h	Extended activity. Expensive.
Trimethoprim-sulfonamide	15–30 mg/kg, PO, IV	12 h	Cheap. Broad spectrum. Limited efficacy in treating septicemia in foals.

- Weight in excess of 20 kg—25 mL/kg/d

Neonates with high ongoing losses, such as those with diarrhea or gastric reflux, can have higher fluid requirements.

Care should be taken to prevent administration of **excess sodium** to foals because they have a limited ability to excrete sodium. The recommended intake is 2 to 3 mEq/kg/d, and this includes sodium administered in parenteral fluids. One liter of isotonic sodium chloride provides a 50-kg foal's sodium requirements for 1 day.

A suitable maintenance fluid for foals is isotonic dextrose (5%) with supplemental potassium (10 to 40 mEq/L).

Respiratory Support

Respiratory failure, evidenced by elevated arterial P_{CO_2} and decreased P_{O_2}, may be a result of depressed central activity, weakness of respiratory muscles, or lung disease. Regardless of the cause, should the hypoxemia become sufficiently severe, oxygenation must be improved by increasing respiratory drive, increasing the inspired oxygen tension, or employing mechanical ventilation. Foals should always be maintained in sternal recumbency to allow optimal respiratory function.

Provision of respiratory support should be considered when the arterial P_{O_2} is less than 60 mm Hg (8 kPa) and the arterial P_{CO_2} is more than 60 mm Hg (8 kPa) in a foal in sternal recumbency. Pharmacologic respiratory stimulants have only a very short duration of action and are of limited use. Nasal insufflation of oxygen is achieved by placing a nasopharyngeal tube and providing oxygen at a rate of 5 L/min.

Mechanical ventilation is useful for maintaining oxygenation in foals with botulism, with more than 80% of foals surviving in one small study. However, this intervention requires considerable expertise and sophisticated equipment. The prognosis is much worse for foals with diseases of the lungs that require mechanical ventilation.

Gastroduodenal Ulcer Prophylaxis

Ill neonatal foals are often treated with antacid drugs in an attempt to prevent the development or progression of gastroduodenal ulcers, although the efficacy of this approach is unproven. There is a trend toward not administering antiulcer medications to foals except for those with demonstrated gastric ulceration, in part because of the recognition that critically ill foals often have gastric pH above 7.0, and administration of ranitidine does not affect this pH. (See "Gastric Ulcers in Foals" for further discussion.)

COMMON COMPLICATIONS

Complications of the neonate's disease or its treatment occur frequently:

- Entropion is common in critically ill foals and, although readily treated, can cause corneal ulceration if undetected.
- Aspiration pneumonia occurs in weak foals, often as a result of aggressive bottle feeding or regurgitation of milk around a nasogastric tube.
- Nosocomial infections can be severe and life-threatening and are best prevented by strict hygiene and asepsis.
- Septic synovitis/arthritis occurs as a consequence of bacteremia and should be treated aggressively.
- Omphalitis and omphalophlebitis occur and can be an undetected cause of fever and relapse. These are best detected by ultrasonographic examination of the abdomen.
- Patent urachus, evident as urine at the navel, usually resolves with time and local treatment.
- Uroperitoneum as a result of urachal rupture occurs in critically ill foals and should be suspected in any ill foal that develops abdominal distension.
- Angular limb deformities and excessive flexor tendon laxity occur frequently in ill neonatal foals but usually resolve with minimal symptomatic treatment as the foal recovers its strength.

PROGNOSIS

The prognosis for critically ill neonates depends on many factors, including the

nature and severity of the disease, facilities available for care, and the expertise of the personnel caring for the neonate. There is a consensus that the recovery rate for severely ill foals has improved over the last decade because of provision of better care. There are reports of survival rates of around 80% for foals treated at a specialized intensive care unit. However, the high cost of providing care for these animals has prompted studies to determine outcome, as a means of deciding whether, financially, treatment is warranted. Surviving Thoroughbred foals do not differ from siblings with regard to percentage of starters, percentage of winners, or number of starts, but surviving foals achieve significantly fewer wins and total earnings.[25]

The increased number of foals being treated intensively has resulted in prospective studies of outcome. The prognosis for athletic activity for foals with septic arthritis is poor. Thoroughbred foals with **septic arthritis** have odds of 0.28 (95% CI 0.12 to 0.62; roughly one-quarter of the likelihood) for racing compared with a cohort of healthy foals. Multisystemic disease, in addition to the presence of septic arthritis, decreased the likelihood of racing to one-tenth that of healthy foals (OR 0.12, 95% CI 0.02 to 0.90). Affected foals that survive take almost 40% longer to race for the first time. Approximately 30% to 48% of affected Thoroughbred foals eventually race, compared with approximately 65% of normal foals.

Attempts to determine prognostic indicators for survival of foals have been partially successful, but they tend to be most applicable to the intensive care unit in which they were developed. The common theme is that sicker foals are less likely to be discharged from the hospital alive.

Characteristics of foals that are more likely to survive include ability to stand when first examined, normal birth, white blood cell (WBC) count in blood that is within or above the reference range, lack of dyspnea, normal plasma fibrinogen concentration, and short duration of disease. The odds of a hospitalized neonatal foal surviving can be calculated using the following formula:

$$\begin{aligned} &Logit\,(Probability\ of\ survival) \\ &= -0.3072 - 2.0115\,(Cold\ extremities) \\ &\quad - 0.8166\,(Prematurity) \\ &\quad - 0.7685\,(\geq 2\ Infection/ \\ &\quad inflammation\ sites) + 0.9877\,(IgG) \\ &\quad + 1.1331\,(Glucose) + 0.9043\,(WBC) \end{aligned}$$

In addition, the survival odds can be summarized in a much more useful form by the methods shown in Tables 19-8 and 19-9. An app to calculate survival probabilities is available for Android phones.[26]

Table 19-8 Method for calculating survival score in hospitalized neonatal foals[1]

Variables	Score	
Cold extremities	No	Yes
	2	0
Prematurity (<320 days)	No	Yes
	1	0
≥2 infection/ inflammation sites	No	Yes
	1	0
IgG (mg/dL)	<400	≥400
	0	1
Glucose (mg/dL)	<80	≥80
	0	1
WBC × (10^3/μL)	≤4	>4
	0	1
TOTAL SCORE		

Table 19-9 Probability of survival for hospitalized neonatal foals with survival scores calculated according to table 19-8

Total foal survival score	Probability of survival
0	3%
1	8%
2	18%
3	38%
4	62%
5	82%
6	92%
7	97%

FURTHER READING

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STILLBIRTH/PERINATAL WEAK-CALF SYNDROME

SYNOPSIS

Etiology Uncertain; probably multiple etiologies and multifactorial.

Epidemiology Most commonly several cases on a farm; several farms affected in a geographic region in a single season; problem may not occur for several years and then occur as "epidemic" in a region.

Clinical findings Calves may be born weak and unable to stand. More commonly, they are born apparently normal and stand but subsequently collapse with hypothermia and die within a few hours of birth.

Lesions Petechial hemorrhages, subcutaneous edema, and hemorrhage commonly in the subcutaneous tissue of the carpal and tarsal joints.

Diagnostic confirmation Specific to cause.

Treatment Supportive.

Control Specific to cause.

HISTORICAL ASPECTS

A syndrome of newborn calves called *weak-calf syndrome* was first recognized in Montana in 1964. It has been recognized throughout the United States and other countries since then, and it is considered a major economic loss in beef cattle herds. In the earlier descriptions of the syndrome, calves were affected by 10 days of age, and approximately 20% were affected at birth. Morbidity ranged from 6% to 15%. In some herds, sporadic abortions occurred before calving season of the herd began. In some cases, affected calves died within minutes after being born with varying degrees of obstetric assistance.

In calves that survived for a few days, clinical findings included lassitude, depression, weakness, variable body temperature, a reddened and crusty muzzle, lameness, reluctance to stand, enlargement of the carpal and tarsal joint capsules along with periarticular subcutaneous swellings, and a hunched-up back if they stood. Diarrhea occurred in some calves after a few days of illness, but it was not a major clinical finding. Treatment was ineffective, and the case fatality rates ranged from 60% to 80%.

At necropsy, the prominent lesions were hemorrhage and edema of the subcutaneous tissues over the tarsal and carpal joint regions and extending distally. Polysynovitis with

hemorrhagic synovial fluid often containing fibrin was also common. Erosive and hemorrhagic lesions of the forestomaches and abomasum also occurred. Several different pathogens were isolated from these calves, but no consistent relationship between the pathogens and the lesions was ever determined.

In retrospect, the case definitions were not well described, and it is probable that several different diseases of newborn calves were lumped into the enigma of weak-calf syndrome. As more detailed clinical and laboratory examinations of sick newborn calves have been done over the years, some of the causes of the original syndrome have been identified as specific diseases of newborn calves.

Widely ranging clinical and pathologic findings have been associated with weak-calf syndrome. In the most common situation, calves are born weak and die within 10 to 20 minutes after birth; sometimes they live for up to a few days. At necropsy there are no obvious or only few lesions to account for the illness. Calves that are weak after birth because of traumatic injuries associated with dystocia or other significant lesions can be accounted for according to the nature and severity of the lesions. Reports from Northern Ireland in recent years indicate that in dairy herds the incidence of weak-calf syndrome has ranged from 10% to 20% of all calves born. Field observations in problem herds found that the gestation period is of normal duration, but parturition is usually prolonged, with the first and second stages of labor lasting 24 hours. Affected calves usually are born alive but are unable to sustain breathing following birth. Despite resuscitation efforts, they commonly die within 10 minutes, often accompanied by prominent uncoordinated movements of the limbs. Some calves are stillborn, and whether or not this is a variation of the syndrome is uncertain. In a report from the United Kingdom, the syndrome occurred in calves born from heifers and was characterized by failure to breathe at birth or breathing with difficulty, and/or failing to move after birth, and failure to suck. The term *stillbirth/perinatal weak-calf syndrome* has been suggested as more appropriate.

Dummy-Calf Syndrome

A variation of weak-calf syndrome is dummy-calf syndrome, which has been reported in the southern United States. Affected calves appear normal at birth and are generally alert, but they lack the instinct or the desire to seek the teat or suck after birth and for up to several hours later. The syndrome may occur in calves of any birth weight. The incidence has been highest in purebred Brahman females, but it has also occurred in Aberdeen Angus, Hereford, Chianina, and Brown Swiss breeds of cattle. Field observations indicate that affected calves did not stand for up to 1 to 2 hours after birth to initiate teat-seeking behavior. Dummy calves appear to lack the sensitivity to teat-seek, and if they fail to locate a teat by about 4 to 5 hours after birth, they commonly lose the sucking reflex and then require intensive nursing care by bottle feeding to initiate sucking. In calves that fail to suck and ingest colostrum, hypothermia, hypoglycemia, and neonatal infections are common complications. Concurrently, the dam loses interest in the calf and may abandon it.

ETIOLOGY AND EPIDEMIOLOGY

The etiology of weak-calf syndrome is unclear, but several epidemiologic observations have suggested some possible causes. These include the following:

- Fetal infection near term
- Underdevelopment because of nutritional inadequacy of the maternal diet during pregnancy
- Placental insufficiency
- Maternal dietary deficiencies of selenium and vitamin E
- Hypothyroidism
- Traumatic injuries associated with dystocia and excessive force during obstetric assistance
- Fetal hypoxia from prolonged parturition

Fetal Infections

Fetal infections in the last few days before term can result in stillbirth or weak calves that may die within hours or days after birth. In one series of 293 weak calves in Northern Ireland, **leptospiral infection** was present in 25% of the calves. Calves in which leptospiral antigen was detected in the placenta were significantly lighter by an average of 6 kg to 10 kg than calves with no antigen in the placenta. Calves infected with *Leptospira* in utero were more likely to be infected by *T.* (formerly *Arcanobacterium) pyogenes* or *Bacillus* species, and infection of the placenta is associated with a lower body weight. The adrenal gland, lung, and placenta are the most useful tissues to examine for leptospiral antigen.

Bovine viral diarrhea (BVD) virus infection has been identified in several herds with high occurrence rates of weak-calf syndrome. Effects of intrauterine infection with this virus will depend on the stage of pregnancy at which infection occurs, but birth of stillborn, weak, or dummy calves certainly warrants taking this differential into consideration (see also "Bovine Viral Diarrhea").

An unidentified type of adenovirus has been associated with weak-calf syndrome on a large dairy farm in Israel. At birth the calves were reluctant to suck or drink colostrum and were force-fed colostrum with an orogastric tube. Affected calves were weak at birth and unable to rise without assistance; when forced to move they walked stiffly, suggestive of polyarthritis. An adenovirus was detected in the feces, synovial fluid, and aqueous humor of affected calves.

Maternal Nutritional Deficiency Causing Fetal Underdevelopment

Hypothyroidism as a result of iodine deficiency in the pregnant dam has been considered on the basis of thyroid hyperplasia in some calves. Analysis of the laboratory data from 365 calves that died from the stillbirth/perinatal weak-calf syndrome in Ireland found some differences between calves with abnormal versus normal thyroid glands. Glands weighing more than 30 g were probably abnormal. Abnormal glands were heavier, constituted a greater percentage of the calf's body weight, and had a lower iodine concentration. A higher proportion of calves with an abnormal thyroid gland had uninflated lungs and pneumonia. Abnormal thyroid glands had a lower selenium concentration in the kidneys.

Hypothyroidism as a result of iodine deficiency can be caused by either inadequate dietary iodine supply or the presence of goitrogens in feed. Goitrogens are substances that impair thyroid hormone synthesis, either by inhibiting iodine uptake (cyanogenic goitrogens) or by inhibiting organic binding of iodine by the thyroid glands (goitrogens of the thiouracil type).[1]

However, the experimental reproduction of iodine deficiency in pregnant heifers by feeding an iodine-deficient diet over the last 4 to 5 months of pregnancy resulted in clinicopathologic changes and pathologic changes in the thyroid glands of both the heifers and their calves, but all calves in the iodine-deficient group were born clinically normal.

Because selenium plays a role in the function of the thyroid glands, selenium deficiency can cause hypothyroidism despite adequate dietary iodine supply. **Maternal dietary deficiency of selenium** in pregnant cattle has also been examined, but field trials have failed to show any protective effect from the parenteral administration of pregnant cattle with selenium. The parenteral administration of both selenium and iodine to pregnant cattle did not have any effect on the incidence of the syndrome between treated and untreated herds; the incidences were 7.9% and 7.4%, respectively.

A general nutritional inadequacy in the maternal diet can result in underdevelopment of the fetus and the birth of smaller-than-normal calves, but the deficiency usually must be grossly inadequate. A clinical trial showed that feeding a protein-restricted ration (7% crude protein) during the last trimester of pregnancy resulted in 11.4% lower birth weights than in control animals and in compromised thermogenic ability of the newborn calves, which has been proposed as a contributing factor to perinatal mortality of calves.[2] Another study

reported a selective decrease in absorption of colostral IgG_1 and IgG_2 from the gut in calves from heifers fed protein-deficient diets during the last trimester of pregnancy, which implies a higher risk for FTPI in these calves.[3]

Placental Insufficiency

Intrauterine growth retardation associated with feto-placental dysfunction has been described in Japanese Black beef calves.[4] Affected calves were weak when born at term and were underweight compared with normal calves. Anemia as a result of bone marrow dysfunction was present in affected calves and presumably was associated with intrauterine growth retardation. Thymic hypoplasia is another common finding in Japanese Black calves that died during the perinatal period, which also has been attributed to intrauterine growth retardation and is thought to contribute to perinatal weak-calf syndrome, which has a high occurrence rate in this breed.[4,5] There is some evidence that an immune inadequacy based on T-lymphocyte function may be associated with weak-calf syndrome in Japanese Black calves, which could be related to the thymic hypoplasia because the thymus is the site of T-cell maturation.

Dams delivering weak calves also had lower serum concentrations of estrone sulfate during late pregnancy than those of normal calves, suggesting a feto-placental dysfunction. The dysfunction was influenced by sires and maternal families.

Fetal Hypoxemia

Fetal hypoxemia resulting from prolonged parturition or dystocia may be a cause or contributing factor to weak-calf syndrome. Various predisposing factors can cause prolonged interference with fetal blood or oxygen supply, which can result in death during delivery or shortly after.

Examination of blood-gas values in newborn calves has shown that a prolonged parturition or delivery terminated by forced extraction results in a severe acidemia as a result of oxygen deprivation and ensuing anaerobic glycolysis with lactate accumulation in combination with hypercapnia, resulting in respiratory acidosis. As blood pH drops, first vitality is reduced, subsequently vital organs such as the brain are damaged, and ultimately the fetus dies.

The bovine fetus appears relatively susceptible to hypoxia and hypercapnia, which has been studied experimentally by clamping the umbilical cords of fetuses for 4 to 8 minutes, at 24 to 48 hours before expected birth, followed by a cesarean section 30 to 40 minutes later. Calves born following this procedure may die in 10 to 15 minutes after birth or survive for only up to 2 days. Under these experimental conditions, fetuses can survive anoxia for 4 minutes, but most will die following 6 or 8 minutes of anoxia.[6] During the clamping there is also increased fetal movement and a release of meconium that stains the calf and the amniotic fluid. Those that survive for a few hours or days are dull and depressed, cannot stand, and have poor sucking and swallowing reflexes, and their temperatures are usually subnormal. They respond poorly to supportive therapy. Some calves whose umbilical cords were clamped for 4 minutes were born weak and made repeated efforts to raise their heads and move onto the sternum, but they were unable to maintain an upright position for long. These calves become hypothermic and dull, and their sucking and swallowing reflexes are present but weak. These calves are usually too weak to suck the cow even when assisted, and they commonly develop diarrhea and other complications.

Dystocia and Traumatic Injuries at Birth

Over 50% of perinatal mortality is generally attributed to dystocia, and dystocia may be an important contributing factor to weak-calf syndrome because of fetal hypoxia or traumatic injuries associated with obstetric assistance.[7] In a study of 13,296 calvings over a period of 15 years in two research herds in Montana, calf mortality as a result of dystocia accounted for the single largest loss category through the first 96 hours postpartum. Reported ORs vary widely (2.7 to 14.6), but they suggest that calves requiring assisted delivery had a 2.7 to 14.6 higher risk of death in the perinatal period than spontaneously born calves.[8] At necropsy of the calves that died as a result of dystocia, the findings included a froth-filled trachea, nonfunctional lungs, bruises, contusions, hemorrhages, bone fractures, and joint dislocations. It was concluded that the provision of adequate obstetric assistance at the right time could have reduced the mortality associated with dystocia.

Traumatic injuries of calves at birth are caused primarily by the mechanical influence of traction during delivery and can result in asphyxia and a high perinatal mortality rate. Excessive traction is the most important cause of rib and vertebral fractures in the calf during dystocia. A series of 235 calves that died perinatally were examined by necropsy to determine the possible causes of death related to dystocia. Most of the parturitions were protracted and needed veterinary assistance, and 58% of the calves had pathologic evidence of asphyxia. Calves delivered by extraction had pathologic evidence of asphyxia more often than those born unassisted or delivered by cesarean section. Intrapulmonary amniotic material may be present in the lungs, representing evidence of perinatal respiratory distress. The aspiration of small amounts of amniotic fluid with or without meconium is common in calves and is not associated with hypoxemia, respiratory acidosis, or failure of passive transfer.

Premature Expulsion of Placenta

Premature expulsion of the placenta has been associated with perinatal calf mortality. Field observations indicate that the majority of affected fetuses die of fetal hypoxia during stage 2 of calving. The most significant risk factor associated with premature expulsion of the placenta was fetal malpresentation and malposture. Prolongation of the second stage of parturition allows for sufficient detachment of the placenta for it to occupy the posterior part of the genital tract. The placenta is frequently expelled together with the calf. In one series of cases, there was no significant relationship between the occurrence of premature expulsion of the placenta and parity, calving difficulty, previous calving history, or sex of the calf.

NECROPSY FINDINGS

All calves that die should be examined by necropsy to identify possible causes. It is important to establish if there is one disease complex or several different diseases of newborn calves.

In the weak-calf syndrome described in Northern Ireland, at necropsy many calves had petechial hemorrhages in the thymus gland, on the ventricular epicardium, and in the parietal pleura and endocardium. These lesions were similar to those present in animals that died of acute terminal asphyxiation. The gasps made in response to asphyxia in utero result in amniotic fluid being inhaled into the respiratory tract. In one study, 84% of stillborn calves had these lesions of asphyxia. It is well established that asphyxiation during birth is a major factor in intrapartum stillbirth in piglets and contributes to early postnatal mortality. Froth may be present in the caudal trachea of some calves that die within 10 to 20 minutes after birth.

Varying degrees of subcutaneous edema of the head and/or bruising of the rib cage are also common. Fractures of the ribs are common, accompanied by intrathoracic hemorrhage. Vertebral body fractures occur commonly at the thoracolumbar region and may be accompanied by intraabdominal hemorrhage. The lungs may be inflated normally, partially inflated, or not inflated. Severe bruising and hemorrhage occur around the costochondral junctions, at the sternal extremities of the costal cartilages, and over the sternum and shoulder regions. In some cases, the traumatic lesions are severe and may involve primarily the right side of the rib cage. Severe subcutaneous hemorrhage and edema may be present over the carpal and fetlock joints as a result of the pressure applied by the obstetric chains or ropes.

In the syndrome described in the United States, the lesions either appeared at birth or developed in the first few weeks of life. At necropsy the prominent lesions are marked edema and hemorrhages of the subcutaneous tissues over the carpal and tarsal joints

and extending distally down the limbs. The synovial fluid may be tinged with blood and contain fibrinous deposits. Erosions or ulceration of the gastrointestinal tract, petechial hemorrhage of internal organs, involution of the thymus gland, and hemorrhages in skeletal muscle have also been present.

The weak-calf syndrome described in Japanese Black calves was associated with atrophy of the red bone marrow and thymic hypoplasia.[9] Degeneration of brainstem nerve cells, attributed to protracted hypoxia, was also noticed.

Samples for confirmation of diagnosis include the following:

- Bacteriology—fetal liver, lung, stomach content, adrenal gland; placenta (culture); special detection techniques for *Leptospira* antigens
- Histology—fixed placenta, lung, spleen, brain, liver, kidney; maternal caruncle (light microscopy, Immunohistochemistry)

DIFFERENTIAL DIAGNOSIS

Determination of the cause of weak-calf syndrome in a herd is often difficult because the limits of the case definition cannot be determined. Several risk factors may interact to contribute to the disease. The most common definition is a calf that is alive at birth, appears normal otherwise, but either fails to breathe or breathes for less than approximately 10 minutes and then dies. If they survive for several hours or a few days, affected calves are usually in sternal recumbency, depressed, reluctant to stand unassisted, reluctant to walk, and not interested in sucking. They may not respond favorably to supportive therapy.

Case definition

When an epidemic of the disease is encountered, an epidemiologic investigation of the herd is necessary in an attempt to identify possible risk factors.

The patterns of occurrence should be determined:

- Is the problem more common in calves born to heifers than cows? In some situations, the owner may provide more surveillance for the calving heifers and less for the mature cows, with a consequent greater incidence of weak calves born from the cows.
- Is there any evidence that parturition is prolonged in the heifers or the cows? If so, what are the possible reasons?
- How long are heifers and cows in the herd allowed to calve unassisted before obstetric assistance is provided?
- Is it possible that some nutritional, management, or environmental factor is interfering with normal parturition?
- Is the condition more common in male or female calves, and what are the relative birth weights?
- How soon after birth are the calves affected?
- What is the course of the illness after the first clinical abnormalities are noted?
- Is the serologic herd status regarding specific infectious diseases known (e.g., *leptospirosis*, BVD, bluetongue)?
- The veterinarian should make every effort to clinically examine a representative number of affected calves.

TREATMENT

Calves born weak, unable to stand, lacking the instinct to seek the teat, or lacking a suck reflex need intensive care, including force-feeding of colostrum and the provision of warm surroundings to prevent hypothermia and other complications. Affected calves must be assisted to suck the dam normally. Bottle feeding for a few days may be necessary until the calf becomes strong enough to suck the dam on its own.

CONTROL AND PREVENTION

Control and prevention of weak-calf syndrome is based on empirical observations, beginning with insuring **adequate nutrition of the dam** to avoid any possible nutritional factors affecting neonatal calf vitality. The provision of **adequate surveillance at calving time** and competent obstetric assistance when necessary is also crucial to avoid prolonged parturition and fetal hypoxia in calves.

When epidemics of the disease are occurring, the surveillance of calving must be intensified, and it may be necessary to intervene with obstetric assistance earlier than usual. Determination of the cause may require that the veterinarian attend several calvings, make detailed clinical examinations of the length of parturition, and observe the parturition process and the health of the calves at birth.

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DISEASES OF CLONED OFFSPRING

The successful cloning of domestic animals using somatic-cell nuclear transfer has resulted in birth of offspring with a high frequency of clinical abnormalities. Cloning of livestock and horses is achieved by transfer of nuclear material from the cell of an adult animal to the enucleated egg of an animal of the same species (somatic-cell nuclear transfer), with subsequent implantation of the resulting embryo in a surrogate dam and birth of a live, viable offspring. However, the use of nuclear material from somatic cells of adult animals, and from fetal cells, frequently does not result in normal development of the embryo and placenta.

The abnormal development in cloned embryos is a consequence of altered methylation of the genome in transferred nuclear material. This applies particularly for imprinted genes, which are those genes for which only one copy is expressed in the embryo, compared with nonimprinted genes for which both parental copies of the gene are expressed. The lower frequency of expression of imprinted genes (i.e., only one copy, paternal or maternal) is a result of methylation of DNA or chromatin proteins that makes the DNA inaccessible for transcription.[1] Imprinting is a form of epigenetic control of gene expression. To date, 132 imprinted genes have been identified in mice, but only 25, 21, and 14 in cattle, pigs, and sheep, respectively.[1] Imprinted genes encode proteins involved in regulation of many cell processes, including embryonic and neonatal growth and development.[1,2]

In normal reproduction, the paternal genome is demethylated during passage through the oocyte and fusion with the maternal genome. Consequently, the methylation marks of the two genomes (paternal and maternal) are different at the end of the cleavage process. Transfer of somatic nuclear material into an enucleated oocyte results in exposure of both genomes to the active demethylating process in the cytoplasm of the oocyte and uniform or variable demethylation of both genomes. The loss of these parent-specific epigenetic markers results in widespread dysregulation of imprinted genes and subsequent abnormalities in the placenta, fetus, and newborn. Imprinting marks (methylation) are erased during early development, and reprogramming of somatic-cell nuclei used in cloning and these abnormalities in epigenetic control of expression of imprinted genes result in biallelic expression of imprinted genes.[3] The loss of epigenetic control of imprinted genes causes at least some of the abnormalities common in cloned ruminants, including large-offspring syndrome (LOS).[3]

A small proportion of transferred blastocysts develop in viable animals. For cattle, of 134 recipients that received blastocysts, 50

were pregnant 40 days after blastocyst transfer, and 23 had full-term pregnancies. For all species studied, fewer than 3% of cloned embryos result in birth of viable animals. Abnormalities in the placenta and newborn cloned animals are reported for cattle and sheep, but are less frequently reported, if at all, for pigs and equids (horses and mules). Factors influencing the risks of abnormalities in newborns include the source of the nuclear material, type of in vitro culture media, coculture with somatic cells, hormonal treatments, and manipulation of the embryo.[1,4] The frequency of birth of live animals born after somatic-cell nuclear transfer from well-differentiated tissue (e.g., fibroblasts) or fetal somatic cells is lower than after nuclear transfer from embryonic cells (7%, 15%, and 34%, respectively).

The cause of placental, fetal, and neonatal abnormalities is abnormal expression of imprinted genes as a consequence of transfer of nuclear material from differentiated somatic cells,[5] conditions and media used for maintenance and culture of cytoplasts and blastocysts, and techniques used for handling cells.[3,6-8] The key abnormality is loss of methylation of imprinted genes contributed by each parent, with subsequent biallelic expression of these genes. There is debate about which epigenetic or genetic abnormalities underlay the development of placental and fetal abnormalities. Aberrant hypomethylation of IGF-2 and CDKC1C genes has been identified in calves with LOS and results in biallelic expression in the liver and placenta of affected animals.[1] Abnormalities in embryologic development of vasculature is identifiable early during embryogenesis in calves and might be the defect underlying pulmonary, circulatory, and umbilical abnormalities in cloned calves.[9] Furthermore, there is decreased expression of genes in the lungs of cloned goats that do not survive compared with those of healthy kids. Compared with normal goats of the same age from conventional reproduction, expression of 13 genes (BMP4, FGF10, GHR, HGFR, PDGFR, RABP, VEGF, H19, CDKNIC, PCAF, MeCP2, HDAC1, and Dnmt3b) decreased in transgenic cloned goats that died at or shortly after birth.[6] Expression of eight genes (FGF10, PDGFR, RABP, VEGF, PCAF, HDAC1, MeCP2, and Dnmt3b) decreased in fetal death of transgenic cloned goats.[6] A comprehensive list of genes known to be involved in embryogenesis and fetal and placental growth and a description of the effect of decreased expression of these genes are available.[10]

Clinical findings in cloned calves and lambs include abortion, placental abnormalities, large birth size, poor extrauterine viability, respiratory disease, cardiovascular abnormalities, and neurologic disease compatible with neonatal encephalopathy. LOS is confined to ruminants and is characterized by overgrowth, evident as abnormally high birth weight, enlarged tongue, umbilical hernias, and hyporglycemia.[3] Abortion occurs after day 90 of gestation in 30% to 50% of pregnancies in cattle, resulting from transfer blastocysts containing transferred nuclear material. Abnormalities, including hydroallantois, are present in approximately 25% of advanced pregnancies. **Placental abnormalities** include hydroallantois, a reduction in the number of placentomes (from a normal value of approximately 100 to as few as 26 to 70 in cloned calves), abnormally large placentomes (140 g in cloned calves versus 33 g in conventional calves), and edema of the placenta.[10] Maternal retention of the placenta is common and occurs in most cows. Duration of gestation is probably longer in cloned calves, although the frequent delivery of cloned calves by cesarean section makes assessment of gestational duration difficult. Cloned calves are heavier than conventional calves, often by as much as 25%, a well-recognized part of the **large-offspring syndrome** that affects calves born as a result of reproductive manipulation, including in vitro fertilization. Viability of cloned calves that are born alive (commonly by cesarean section) is less than that of conventional calves; only approximately two-thirds of cloned calves born alive survive more than 1 month, although others have reported better survival. Similar results are reported for horses.

A high proportion of cloned calves have **clinically detectable abnormalities** at or soon after birth, including sepsis, neonatal encephalopathy, respiratory failure, umbilical abnormalities, anemia, flexure contracture, abdominal distension, and renal dysfunction. Respiratory failure is a common finding and might reflect persistent fetal circulation or inadequate surfactant production, as evidenced by the high pulmonary artery pressures and signs consistent with patent ductus arteriosus.[11] Left heart failure, which can also cause pulmonary hypertension, is reported in cloned calves. Umbilical abnormalities are evident as abnormal umbilical cord structure (multiple arteries and veins) and large size, with a high risk of hemorrhage from the umbilical cord after birth. Cloned calves have higher body temperatures than do conventional calves.

Of 27 cloned calves delivered alive, 7 were bradypneic or apneic at birth, 5 had flexural limb deformities, and at least 23 had enlarged umbilical cords. The calves were acidotic at birth as a result of both respiratory and lactic acidosis. Calves had normocytic hypochromic anemia, stress leukogram (leukocytosis, neutrophilia, and lymphopenia), and hypoproteinemia (with both hypoalbuminemia and hypoglobulinemia) and had increased serum creatinine concentration.[12] Three of the calves did not develop other clinical signs and were considered healthy after birth, whereas 22 had at least one important clinical abnormality detected during the week after birth. Twelve of the calves developed omphalitis. Fourteen of the calves died or were euthanised.[12]

Hematologic abnormalities include anemia and decreased mean corpuscular volume. Biochemical abnormalities include hypoxemia, azotemia, and hypoglycemia. Plasma leptin and IGF-2 concentrations are higher, and thyroxine lower, in cloned calves. Serum cortisol and adrenocorticotropic hormone (ACTH) stimulation tests do not differ between cloned and conventional calves. Cloned calves can mount normal immune responses.[13] Failure of transfer of passive immunity can occur if calves are unable to suckle or are not administered colostrum or plasma.[12]

Necropsy examination reveals placentomegaly, presence of excess pleural and peritoneal fluid, hepatomegaly, interstitial pneumonia or pulmonary consolidation and alveolar proteinosis, right ventricular dilation, and hepatocellular vacuolation.

Treatment is supportive and directed toward correcting hypoxemia and providing nutritional, fluid, and environmental support (see earlier discussion).

There are currently no recognized methods for preventing these abnormalities, but incremental improvements in methodology and culture techniques will continue to result in fewer cloned offspring with these abnormalities.

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EQUINE NEONATAL MALADJUSTMENT SYNDROME (NEONATAL ENCEPHALOPATHY, DUMMY FOAL, BARKERS, AND WANDERERS)

This is a syndrome of foals less than 36 hours of age characterized by a spectrum of changes in mentation ranging from failure

to suckle, abnormal behavior, and seizures through coma in otherwise apparently healthy foals. The syndrome is defined by the clinical abnormalities and not by a common etiology.

ETIOLOGY

The clinical signs associated with this syndrome can be produced by a number of diseases, each of which has its particular etiology. Diseases that contribute to this syndrome include antenatal, natal, or postnatal hypoxia;[1] a range of congenital abnormalities (hydrocephalus, hydrencephalus,[2] and such); metabolic disorders;[3] placental abnormalities;[4] intracranial hemorrhage; prematurity; and thoracic trauma. Fetal or perinatal hypoxia has achieved some prominence as a cause of neonatal maladjustment syndrome in the absence of consistent demonstration of lesions of hypoxia on histopathologic examination of foals. There are isolated cases in which histologic evidence of hypoxia exists, but these are the exception rather than the rule. Finally, most foals with neonatal maladjustment syndrome improve rapidly and completely recover within several days—a clinical course not expected with neonatal or perinatal asphyxia in other species.

Recent evidence implicates a role of neuroactive progestagen derivatives in the etiopathogenesis of neonatal maladjustment syndrome.[5,6] Plasma concentrations of these neuroactive steroids in foals are high immediately after birth and decline rapidly in healthy foals, but not in foals with neonatal maladjustment syndrome.[5] Foals with neonatal maladjustment syndrome and foals with other illness have higher concentrations of progestagen derivatives than do healthy foals.[5] Plasma concentrations of progestagen derivatives decline in sick foals that do not have neonatal maladjustment syndrome, but not in foals with the syndrome.[5] Progestagen derivatives include progesterone, pregnenolone, androstenedione, dehydroepiandrosterone, and epitestosterone.[5] Evidence from other species and limited experimental evidence in foals indicate that allopregnanolone infusion induces changes in mental status that mimic those seen in foals with neonatal maladjustment syndrome.[6] It is proposed that a subset of foals with signs of neonatal maladjustment syndrome have disease attributable to persistence of the fetal hypothalamic–pituitary–adrenal axis after birth.

EPIDEMIOLOGY

The disease is sporadic and occurs worldwide, with an annual **incidence** in foals of less than 1%.[7] Foals of either sex and of any breed born to mares of any age or reproductive history can be affected. The **case fatality rate** is very low for appropriately treated foals without other systemic illness.

PATHOGENESIS

Hypoxia resulting from intracranial vascular accidents, asphyxia at birth, or placental insufficiency before birth damages the central nervous system, causing a wide variety of signs of neurologic dysfunction.

A proposed pathogenesis for foals with persistently high plasma concentrations of progestagen derivatives after birth is failure of the foal's hypothalamic–pituitary–adrenal axis to rapidly adjust to extrauterine life.[6] In utero, foal movement and activity is suppressed, presumably at least in part by high concentrations of neuroactive progestagens. At birth in healthy foals there is a rapid reduction in concentration of these hormones coincident with increases in activity of the foal. Progestagen derivatives, some of which can cross the blood–brain barrier, modulate the activity of the $GABA_A$ receptor and at high concentrations completely inhibit its activity, providing a potential explanation for the somnolence and other signs displayed by foals with neonatal maladjustment syndrome and high plasma progestagen concentrations.[5]

Neurologic abnormalities and a failure to nurse result in a failure of the transfer of maternal immunoglobulins, which predisposes the foal to septicemia and hypoglycemia. Failure to nurse also results in hypoglycemia and malnutrition.

CLINICAL SIGNS

Foals that are abnormal at birth can display a range of behavioral abnormalities, from lack of suckle reflex to convulsions with extensor rigidity. The placenta of affected foals is often abnormal, or there is a history of prolonged parturition. Affected foals either do not develop or lose the suck reflex, have no affinity for the mare, and are unable to locate the udder or teat. Aimless wandering and a characteristic "barking" vocalization are sometimes present. Recumbent foals struggle wildly and in an uncoordinated fashion to stand. Convulsing foals usually display opisthotonos with extensor rigidity. Other signs of convulsive activity include facial twitching and grimacing, nystagmus, rapid blinking, sucking, chewing, and drooling. Between episodes foals are usually depressed or somnolent. Affected foals display little or no interest in the mare. Convulsing foals are tachypneic, tachycardic (>180 bpm), and hyperthermic (>39° C, 102° F) during and immediately after convulsions. It is important to recognize that the severity of clinical signs varies from very mild (foals are often described by owners as being a bit slow or dimwitted) through to grand mal seizures.

Foals that are normal at birth can develop signs by 24 hours of age. The signs are similar to those described previously, with the exception that the foals are initially able to ambulate. It is important to realize that healthy newborn foals lack a menace reflex, have a hypermetric gait and intention tremor, and become flaccid when restrained. The reflex response of healthy foals to restraint by a handler placing one arm under the foal's neck and another around the buttocks and squeezing is to become "floppy" and somnolent.[6] Foals restrained in this way become immobile, lie down, and have an increased pain threshold during restraint.[6]

Affected foals can take days to weeks to recover completely. Blind foals that do not have ocular lesions can take as long as 4 to 6 weeks to regain vision.

Ancillary testing is not usually indicated unless the foal fails to respond after approximately 7 days. At that time, CT or MRI examination of the brain might be indicated to detect congenital anomalies such as hydrocephalus. Examination of CSF should be performed in any foal with signs of central nervous system dysfunction in the presence of fever or other signs of sepsis.

CLINICAL PATHOLOGY

There are no routine hematologic or serum biochemical abnormalities characteristic of the disease, although it is prudent to conduct such examinations to eliminate other diseases; common characteristics are as follows[3]:

- Affected foals usually have **failure of transfer** of maternal immunoglobulins (serum IgG < 400 mg/dL).
- They may be **hypoglycemic** (<80 mg/dL, 4 mmol/L).
- **Cerebrospinal** fluid is often normal, although it may contain red blood cells or appear xanthochromic as a result of bleeding.

Detection of **biomarkers of brain injury** has been investigated. Plasma concentrations of **ubiquitin C-terminal hydrolase** (UCHL1) are higher (6.57, range 2.35 to 11.9 ng/mL) in foals with signs of neonatal maladjustment syndrome (defined as neonatal hypoxic-ischemic encephalopathy in the study) than in healthy foals (2.52, range 1.4 to 4.01 ng/mL).[8] The sensitivity and specificity for diagnosis of neonatal maladjustment syndrome based on a cutoff of ubiquitin C-terminal hydrolase concentrations in plasma of 4.01 ng/mL were 70% and 94%, respectively.[8]

Measurement of **plasma progestagen concentrations** of foals with signs of neonatal maladjustment syndrome might prove to be useful in diagnosis of the disease. Foals with high concentrations of progestagens could be treated appropriately, and those with low or normal concentrations could be further investigated for other diseases such as intracranial hemorrhages or hydrocephalus.

DIAGNOSTIC CONFIRMATION

Definitive diagnosis of the disease is difficult and is based on exclusion of other diseases that can cause similar signs and, at necropsy, demonstration of intracranial lesions consistent with the disease.

NECROPSY FINDINGS

Gross changes are typically limited to diffuse pulmonary congestion with a variable degree of atelectasis. In cases in which dystocia has been a contributing factor, fractured ribs and foci of subcutaneous edema and hemorrhage are sometimes noted. Occasionally, macroscopic cerebral hemorrhages are visible. Histologically, the key findings are hemorrhagic foci within the brain and areas of ischemic necrosis in the cerebral cortex. Meconium and other components of aspirated amniotic fluid accompanied by atelectasis and a mild inflammatory response may be present within the lung. In less affected foals the brain lesions are restricted to hemorrhage, cerebral swelling, and edema. Some affected foals subject to necropsy examination have evidence of intracranial vascular accidents, but it must be recognized that this is a biased sample; many foals recover from the disorder. Affected foals that are euthanized for financial or management reasons often have no detectable lesions in the brain.

Samples for Postmortem Diagnostic Confirmation

Samples for postmortem diagnostic confirmation include formalin-fixed brain, including cerebral cortex, cerebellum, and brainstem, and lung for light microscopic examination.

DIFFERENTIAL DIAGNOSIS

The disease must be differentiated from other diseases that cause neurologic or behavioral abnormalities in foals, including sepsis; renal, hepatic, or gastrointestinal disease, which can occur secondary to fetal hypoxia; hydrocephalus; hypoglycemia; meningitis; neonatal isoimmune hemolytic anemia; and prematurity, dysmaturity, or immaturity (Table 19-10).

TREATMENT

The principles of treatment are as follows:

- Control of convulsions
- Treatment of cerebral edema and hemorrhage
- Correction of FTPI
- Nutritional support and general nursing care

The management of affected foals is mainly supportive and is a time-consuming and labor-intensive endeavor. Provision of nutritional support, treatment of failure of transfer of maternal immunoglobulins, and nursing care are discussed in detail in the section "Principles of Care of the Critically Ill Neonate."

For other than emergency treatment of seizures, in which **diazepam** (0.1 to 0.4 mg/kg, intravenously, as required) or **midazolam** (0.05 to 0.1 mg/kg IV, as required) are useful, **phenobarbital** (phenobarbitone), **phenytoin,** and **primidone** are the drugs of choice for long-term control of seizure activity. Phenobarbital is administered initially at a dose of 9–20 mg/kg intravenously in 30 mL of isotonic saline infused over 15 to 30 minutes. Maintenance therapy is a similar dose intravenously (7–9 mg/kg IV over 20 min every 8–12 hours) or a lower dose (1–5 mg/kg) orally, every 8 hours, and the dose is adjusted

Table 19-10 Differential diagnosis of comatose ("sleeper") neonatal foals

Disease	Epidemiology	Clinical findings	Clinical pathology	Lesions	Treatment and prognosis
Septicemia	*E. coli, Klebsiella* spp., *Streptococcus* spp., *Salmonella* spp., *Actinobacillus suis,* Equine herpesvirus-1. Failure of transfer of passive immunity.	Abrupt onset of depression, fever, failure to nurse, and recumbency. Later diarrhea, pneumonia, and joint distension.	Culture of organism from blood or lesions (joints, lungs, feces).	Consistent with septicemia. Pneumonia. Septic synovitis, arthritis, and osteomyelitis.	Broad-spectrum antibiotics, supportive care (see "Principles of Providing Care to the Critically Ill Neonates"). Guarded to poor prognosis.
Isoimmune hemolytic anemia	Incompatible mating of Aa + or Qa + stallion with negative mare.	Normal at birth. Subsequent depression, cessation of nursing, exercise intolerance, icterus, and anemia. Hemoglobinuria in severe cases.	Positive Coombs' test to demonstrate immunoglobulin on foal's red cells. Dam's colostrum agglutinates or lyses foal red cells.	Anemia, icterus. Death from anemic hypoxia.	Transfusion of washed dam's red blood cells or of compatible donor (check dam's plasma with donor's red cells). Fair prognosis.
Uroperitoneum	Ruptured bladder, urachus or ureteral defect. Colts 1–3 days of age. Foals of either sex with other systemic diseases.	Normal at birth. Onset of abdominal distension, mild colic, depression, and recumbency. May urinate small volumes.	Peritoneal fluid has high creatinine concentration. Hyperkalemia, hyponatremia, and hypochloremia.	Uroperitoneum. Rupture bladder, urachus or ureter.	Surgical correction AFTER drainage of abdomen and resolution of hyperkalemia with intravenous dextrose or 0.9% NaCl. Good prognosis with appropriate care.
Hypoglycemia	Failure to nurse. Rejection by mare. Mare has no milk (agalactia).	Normal at birth, repeated attempts to nurse. Gradual onset (hours) of weakness and depression.	Low blood glucose concentration (<60 mg/dL, 3 mmol/L).	None. No food in stomach.	Excellent response to feeding or intravenous glucose.
Neonatal maladjustment syndrome	Sporadic.	Onset of abnormal behavior, recumbency, failure to nurse or orient to mare. Aimless wandering and vocalization.	None characteristic. Frequently failure of transfer of passive immunity.	Usually none apparent. Occasional intracranial vascular accidents.	Supportive care (see "Principles of Providing Care to Critically Ill Neonates"). Good prognosis.
Congenital defects	Sporadic.	Depends on nature of cardiac, gastrointestinal, or central nervous system defect.	None.	Consistent with defect.	Usually no treatment. Poor prognosis depending on defect.

to provide control of seizures while minimizing the degree of sedation. Because of the long elimination half-life of phenobarbital in foals (~200 hours) and the transient nature of the disease, once seizure control is achieved, administration of phenobarbital can be discontinued. Drug concentrations will be at or above the target concentration (5 to 30 µg/mL) for several days after the final dose. **Phenytoin** (5 to 10 mg/kg intravenously or orally initially, then 1 to 5 mg/kg every 4 hours) or **primidone** (20 to 40 mg/kg orally every 12 to 24 hours, to effect) are also used to control convulsions.

Definitive demonstration of the presence of cerebral edema or intracranial hemorrhage is impossible without sophisticated imaging devices, such as MRI or CT. However, treatment is often initiated on the basis of clinical signs. None of the treatments has demonstrated efficacy, and some are controversial. **Dimethyl sulfoxide** (DMSO) is given intravenously at 0.5 to 1 mg/kg once or twice daily for 3 days as a 10% solution. **Mannitol** (0.25 g/kg, intravenously as a 20% solution) may be effective in treating cerebral edema, but it is contraindicated if intracranial hemorrhage is present. **Glucocorticoids** (dexamethasone, 0.2 to 1 mg/kg, or prednisone, 1 to 2 mg/kg) might reduce intracranial inflammation and swelling. They might be contraindicated in foals with sepsis.

Magnesium sulfate (0.05 mg/kg per hour for 1 hour, then 0.025 mg/kg/h intravenously for up to 48 hours) is often administered to foals with suspected hypoxic encephalopathy in an attempt to minimize neuronal damage. There is no objective evidence of its efficacy in foals.

Foals with respiratory depression can be administered **caffeine** (10 mg/kg orally once and then 3.0 mg/kg orally q 24 hours). There is objective evidence of the lack of efficacy of this treatment in improving survival or decreasing arterial carbon dioxide tension in foals with a diagnosis of neonatal hypoxia-ischemia.[9] Adverse effects include agitation, hyperesthesia, tachycardia, and convulsions.

Good nursing care is critical in affected foals, and a concerted and persistent effort should be made to encourage the foal to nurse the mare. Encouraging the foal to nurse can be frustrating for the handler and mare, but should be done regularly, about every 4 hours, and preferably when the foal is hungry. Affected foals often begin to nurse quite suddenly. Foals should be provided with nutritional support, such as with mare's milk administered by indwelling nasogastric tube, until they are able to suckle.

Affected foals can require up to 4 to 6 weeks to recover completely, although most do so within 1 week of birth, and hasty decisions regarding euthanasia should not be made without recognition of the sometimes long time required for complete recovery.

CONTROL

Prevention of hypoxia in neonates by close monitoring of the health of the mare and of parturition may reduce the incidence of the disease.

FURTHER READING

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Neonatal Infectious Diseases

SYNOPSIS

Etiology Common infections for each animal species are listed under "Etiology" in the discussion. Most etiologies are bacterial, but some are viral.

Epidemiology Commonly predisposed by management and environmental factors and difficult delivery that increase the exposure risk and load and decrease the resistance of the neonate.

Clinical findings Depending on the pathogen and portal of entry, local infection or septicemia with following localization can occur; signs can be specific for the agent and the affected organ(s).

Clinical pathology White blood cell and differential counts, toxic change, serum immunoglobulin concentrations, blood gas analysis, acute-phase protein concentrations, blood culture.

Necropsy findings Specific to disease.

Diagnostic confirmation Specific to disease.

Treatment Treatment may include antimicrobial therapy, correction of acid–base disturbance, fluid and electrolyte therapy, blood or plasma transfusion, antiinflammatory therapy, and other supportive treatment.

Infection is a common cause of morbidity and mortality in neonates. There are a number of specific infectious pathogens that can cause disease. Other microorganisms normally present in the neonate's environment can become opportunistic pathogens whenever the immunologic status of the neonate is impaired. Maternal immunoglobulins are not transferred transplacentally in ungulates, and the newborns rely on the acquisition of immunoglobulins from colostrum for passive antibody protection.

ETIOLOGY

In domestic farm animals the common infections that can produce disease during the neonatal period are described in the following subsections. (Relative importance and prevalence statistics are not given because these vary from area to area and with differing management systems.)

Calves

- Enteritis associated with enterotoxigenic *Escherichia coli*; *Salmonella* spp.; rotavirus and coronavirus; *Cryptosporidium parvum*; *Clostridium perfringens* types A, B, and C; and occasionally by the virus of infectious bovine rhinotracheitis and bovine viral diarrhea
- Bacteremia and septicemia associated with *E. coli, Listeria monocytogenes, Pasteurella* spp., streptococci, or *Salmonella* spp.

Pigs

- Septicemia with or without localization in joints, endocardium, and meninges associated with *Streptococcus suis, Streptococcus equisimilis, Streptococcus zooepidemicus*, and *L. monocytogenes*
- Bacteremia, septicemia, and enteritis associated with *E. coli*
- Transmissible gastroenteritis, Aujeszky's disease, swine pox, enterovirus infections, and vomiting and wasting disease associated with viruses
- Enteritis associated with *C. perfringens, Campylobacter* spp., rotavirus, and *Coccidia* spp.
- Arthritis and septicemia associated with *Erysipelothrix rhusiopathiae*

Foals

- Septicemia with localization associated with *E. coli, Actinobacillus equuli, Klebsiella pneumoniae, α-hemolytic streptococci, S. zooepidemicus, L. monocytogenes, Rhodococcus equi,* and *Salmonella typhimurium*
- Enteritis associated with *C. perfringens* types A, B, and C; *Clostridium difficile; R. equi; Salmonella spp.; Strongyloides westeri; C. parvum;* and rotavirus.

Lambs

- Septicemia or bacteremia with localization in joints and/or synovia and/or leptomeninges associated with *E. coli, L. monocytogenes,* streptococci, micrococci, *E. rhusiopathiae*, and *Chlamyodophila* spp.
- Enteritis associated with enterotoxigenic *E. coli, Salmonella* spp., rotavirus and coronavirus, and *C. parvum*
- Lamb dysentery associated with *C. perfringens* types B and C

- Gas gangrene of the navel associated with *Clostridium septicum, Clostridium novyi*, and *Clostridium chauvoei*
- Pyemia associated with *Staphylococcus aureus*, *Fusobacterium necrophorum*, and *Trueperella* (formerly *Arcanobacterium) pyogenes*
- Pneumonia, polyserositis, and peritonitis associated with *Pasteurella multocida* and *Mannheimia hemolytica*

The agents listed in the following subsections are recorded as causing neonatal infections but are less common than those listed in the previous subsections and not of as great importance.

Calves

Pseudomonas aeruginosa, *Streptococcus pyogenes, Streptococcus faecalis, S. zooepidemicus, Pneumococcus* spp.; enteritis resulting from *Providencia stuartii, Chlamydophila* spp., *A. equuli*.

Lambs

S. aureus (tick pyemia); enteritis resulting from *E. coli,* rotavirus; pneumonia resulting from *Salmonella abortus–ovis*.

Foals

Enterobacter cloacae, *S. aureus, Pasteurella multocida, P. aeruginosa, T. pyogenes, Serratia marcescens*.

All Species

Nonspecific infections are associated with pyogenic organisms, including *T.* (formerly *Arcanobacterium) pyogenes* and *Fusobacterium necrophorum*; *S. faecalis*, *S. zooepidemicus*, *Micrococcus* spp., and *Pasteurella* spp. occur in all species.

EPIDEMIOLOGY

The occurrence of neonatal disease is broadly influenced by two main factors: the exposure or infection pressure of the infectious agent to the neonate and the ability of the neonate to modulate the infection so that disease does not occur. Some agents are sufficiently virulent in their own right that an exposure can lead to disease. With others, the majority, the defenses of the host must be compromised or the infection challenge must be very high before clinical disease occurs. Management of the neonate has a great influence on both of these factors, and the recognition and correction of these risks is the key to the prevention of neonatal disease in both the individual and the group.

Sources of Infection

Postnatal Infection

The vast majority of infections are acquired by the neonate after birth, directly from the environment into which it is born. The source of infection can be any adult animal present in the maternity area, an infected neonate housed in close proximity, contamination of the environment, or an animal caretaker functioning as mechanical or biological vector. Details for the common neonatal diseases are given under the individual disease headings.

Prenatal Infection

Some bacterial and viral infections that manifest with neonatal disease are acquired in utero and are associated with bacteremia/viremia in the neonate.[1] The majority of these are agents that cause abortion, and neonatal septicemia is only part of the disease spectrum associated with these pathogens. Examples include many of the agents producing abortion in sheep.

Some septicemic infections in **foals**, particularly those associated with *A. equuli*, *S. zooepidemicus*, *Salmonella abortusequi*, and possibly some *E. coli* septicemic infections, are acquired by prenatal infection. If the disease is intrauterine in origin, it reaches the foal's organism via the placenta, probably by means of placentitis resulting from a blood-borne infection or endometritis of the mare.

Viral infections that are acquired in utero are listed in the section on congenital disease.

Routes of Transmission

The **portal of infection** is commonly by oral ingestion, but infection may also occur via aerosol inhalation. Invasive organisms capable of producing bacteremia and septicemia invade through the nasopharynx or through the intestinal epithelium. An alternate route of infection and invasion is via the umbilicus. Routes of **excretion** are via the feces in enteric disease and the nasal secretions, urine, and sometimes the feces in septicemic disease, resulting in contamination of the neonatal environment.

Where neonates are in groups or in close contact, direct transmission by fecal, respiratory secretion, and urine aerosols are common routes for transmission of infection. Neonatal bull calves that are group-housed and that suck one another's navels can transmit infection by this activity.

Risk Factors and Modulation of Infection

Immunity

Neonates are generally more susceptible to infection than their adult counterparts. The calf, lamb, piglet, and foal are born without significant levels of immunoglobulins and possess almost no resistance to certain diseases until after they have ingested colostrum and absorbed sufficient quantities of immunoglobulins from the colostrum. **Failure of transfer of passive immunity** is a major determinant and is discussed under that heading.

Immune Responsiveness

All components of the immune system are present in foals and calves at birth, but the immune system of the newborn animal is less mature than its adult counterpart, at least for the first 30 days of life, and does not respond as effectively to an antigen stimulus.

Immune responsiveness is age-dependent but also varies with the antigen. In colostrum-fed animals, part of the inefficiency of the newborn to produce humoral antibodies following exposure to antigens is the interference from circulating colostral antibody and the downregulation by colostrum of endogenous immunoglobulin production.

Colostrum-deprived calves respond actively to injected antigens and are thought to be immunologically competent at birth with respect to most antigens. Immune competence begins during fetal life, and the age of gestation at which this occurs varies according to the nature of the antigen. The bovine fetus will produce antibodies to some viruses, beginning at 90 to 120 days, and by the third trimester of gestation it will respond to a variety of viruses and bacteria. The lamb will respond to some antigens beginning as early as 41 days and not until 120 days for others. The piglet at 55 days and the fetal foal also respond to injected antigens.

The presence of high levels of antibodies in the precolostral serum of newborn animals suggests that an in utero infection was present, which is useful for diagnostic purposes. The detection of immunoglobulins and specific antibodies in aborted fetuses can be a useful aid in the diagnosis of abortion in cattle.

Exposure Pressure

The exposure pressure is a factor of the cleanliness of the environment of the neonate. The phenomenon of a "buildup of infection" in continual-throughput housing for neonatal animals has been recognized for decades and has been translated to many observations of risk for neonatal disease associated with suboptimal hygiene and stocking density in both pen and paddock birthing areas. Details for the individual species are provided in the section on perinatal disease.

Age at Exposure

With several agents that produce neonatal disease, the age of the neonate at infection and the infecting dose have a significant influence on the outcome. Examples are the importance of age with respect to susceptibility to disease associated with some enteric infections. Disease associated with enteropathogenic *E. coli* and with *C. perfringens* types B and C occurs only in young animals, and if infection can be avoided by hygiene in this critical period, disease will not occur regardless of subsequent exposure. Colostrum-deprived calves show significant resistance to challenge at 7 days of age with strains of *E. coli* that invariably produce septicemic disease if challenged at the time of birth, and isolation of

an immunocompromised neonate is an important factor in its survival. Thus the management of the neonate and its environment is a critical determinant of its health. Age at exposure also varies with the epidemiology of the pathogen, and segregated early weaning is used to reduce transmission of and infection with certain pathogens in pigs.

Animal Risk Factors

Animal risk factors that predispose to infection include those that interfere with sucking drive and colostral intake, such as cold stress and dystocia. These are detailed in the preceding section on perinatal disease.

PATHOGENESIS

The pathogenesis varies with the neonatal infectious disease under consideration and is given for each of these in the special medicine section.

An infection can remain localized at the initial site of infection, as is the case with uncomplicated omphalitis or enterotoxigenic *E. coli* infection, or it can spread by invading the organism (e.g., via the nasopharynx, the gastrointestinal tract, or the umbilical vein or urachus). In the latter case the usual pattern of development is bacteremia followed by **septicemia** with severe systemic signs, or **bacteremia** with few or no systemic signs followed by **localization** in various organs.[2] **Localization** is most common in the joints, producing a suppurative or nonsuppurative arthritis. Less commonly there is localization in the eye to produce panophthalmitis, in the heart valves to cause valvular endocarditis, or in the meninges to produce meningitis.

Secondary lesions often take time to develop, and signs usually appear at 1 to 2 weeks of age. This is especially true with some of the streptococcal infections, in which bacteremia may be present for several days before localization in the joints and meninges produces clinical signs. Bacterial meningitis in newborn ungulates is preceded by bacteremia followed by a fibrinopurulent inflammation of the leptomeninges, choroid plexuses, and ventricle walls, but it does not affect the neuraxial parenchyma. It is proposed that the bacteria are transported in monocytes, which do not normally invade the neuraxial parenchyma.

Dehydration and acid–base and electrolyte imbalance can occur very quickly in newborn animals, whether diarrhea and vomiting (pigs) are present or not, but obviously are more severe when there is fluid loss into the gastrointestinal tract. In gram-negative sepsis the prominent signs are those of endotoxemia.

CLINICAL FINDINGS

The clinical findings depend on which organ systems are affected, the rapidity of growth of the organism, its propensity to localize, and its potential to produce toxemia. Clinical signs are often vague and unspecific in the initial phase of septicemia until the infection localizes and affects one or several organs.[1,2] Organisms that have a low propensity for toxemia present with fever, depression, anorexia, and signs referable to localization. These include endocarditis with a heart murmur; panophthalmitis with pus in the anterior chamber of the eye; meningitis with rigidity, pain, and convulsions; and polyarthritis with lameness and swollen joints. With more virulent organisms there are clinical signs of toxemia and bacteremia, including fever, and advanced stages result in hypothermia, severe depression, obtundation, coma, petechiation of mucosae, dehydration, acidemia, and rapid death.

The clinical and clinicopathologic characteristics of the septicemic foal were detailed in an outbreak of septicemia in colostrum-deprived foals and in the clinical records of 38 septicemic foals admitted to a referral clinic. The major clinical findings included lethargy, unwillingness to suck, inability to stand without assistance but remaining conscious, unawareness of environment and thrashing or convulsing, diarrhea, respiratory distress, joint distension, central nervous system abnormalities, uveitis, and colic. Fever was not a consistent finding.

A **sepsis score** has been developed for foals based on 14 measures related to historical, clinical, and laboratory data (Table 19-11). The score derived from the collective differential scoring of these data has been found to be more sensitive and specific for infection than any parameter taken individually. However, a subsequent study of 168 foals presented to a university hospital found that the sepsis score correctly predicted sepsis in 58 out of 86 foals and nonsepsis in 24 out of 45 foals, resulting in a sensitivity of 67%, a specificity of 75%, a positive predictive value of 84%, and a negative predictive value of 55%, and it was suggested that the score system should be used with care because the low negative predictive value limited its clinical utility.

A sepsis score for calves, based on fecal consistency, hydration, behavior, ability to stand, state of the umbilicus and degree of injection of scleral vessels, and presence of hypoglycemia and abnormal neutrophil cell count, was found to have reasonable predictive value.[3]

The clinical findings specific to individual etiologic agents are given under their specific headings in the special medicine section of this book.

CLINICAL PATHOLOGY

Clinical pathology is used as an integral part of the evaluation of a sick neonate and to help formulate a treatment plan. A major evaluation is to attempt to confirm the presence or absence of sepsis, and this type of evaluation has been developed most successfully in the foal. **Blood culture** is part of this examination, but the time for a positive result limits its value in the acutely ill neonate. Laboratory findings in foals with neonatal sepsis are variable and depend on the severity, stage, and site of infection. **Serial examinations** are commonly used. In examinations relating to the possible presence of septicemia, particular emphasis is placed on the results of the white blood cell and differential counts, the presence of toxic change (toxic granulation and vacuolization), serum immunoglobulin concentrations, arterial oxygen concentrations, the presence of metabolic acidosis, abnormal blood glucose concentrations, and elevated fibrinogen levels.[1,4]

DIFFERENTIAL DIAGNOSIS

- The principles of diagnosis of infectious disease in newborn animals are the same as for older animals. However, in outbreaks of suspected infectious disease in young animals, there is usually a need for more diagnostic microbiology and pathology.
- With outbreaks, owners should be encouraged to submit all dead neonates as soon as possible for a meaningful necropsy examination.
- In addition to postmortem examination, it is necessary to identify the factors that may have contributed to an outbreak of disease in newborn calves, piglets, or lambs, and only detailed epidemiologic investigation will reveal these.

TREATMENT

The first principle is to obtain an etiologic diagnosis if possible. Ideally a drug sensitivity of the causative bacteria should be obtained before treatment is given, but this is not always possible. It may be necessary to choose an **antibiotic** based on the tentative diagnosis and previous experience with treatment of similar cases.

Outbreaks of infectious disease are common in litters of piglets and groups of calves and lambs, and individual treatment is often necessary to maximize survival rate. Supportive fluid and electrolyte therapy and correction of acid–base disturbances are described in detail under "Disturbances of Free Water, Electrolytes, and Acid–Base Balance."

The provision of **antibodies** to sick and weak newborn animals through the use of blood transfusions or serum is often practiced, especially in newborn calves in which the immunoglobulin status is unknown. Whole blood given at the rate of 10 to 20 mL/kg body weight, preferably by the intravenous route, will often save a calf that appears to be in shock associated with neonatal diarrhea. The blood is usually followed by fluid therapy. Serum or plasma can also be given at half the dose rate. The blood should not be taken from a cow near parturition because the circulating immunoglobulins

Table 19-11 Worksheet for calculating a sepsis score for foals less than 12 days of age[1]

Variable	NUMBER OF POINTS TO ASSIGN 4	3	2	1	0	Score for this case
1. Historical data						
a. Placentitis, vulvar discharge before delivery, dystocia, sick dam, induced parturition		Present			Absent	
b. Gestation length (days)		<300	300–310	311–330	>330	
2. Clinical examination						
a. Petechiation or scleral injection (nontraumatic)		Marked	Moderate	Mild	None	
b. Rectal temperature (° C)			>38.9	<37.8	37.9–38.7	
c. Hypotonia, convulsions, coma, depression			Marked	Moderate	Mild	
d. Anterior uveitis, diarrhea, respiratory distress, swollen joints or open wounds		Present			Absent	
3. Hemogram						
a. Neutrophil count (cells × 10^9/L)		<2.0	2.0–4.0 or 8.0–12.0 >12	4.0–8.0		
b. Band neutrophils (cells × 10^9/L)		>0.2	0.05–0.2		<0.05	
c. Toxic changes in neutrophils	Marked	Moderate	Slight		None	
d. Fibrinogen concentration (g/L)			>6.0	4.1–6.0	4.0	
4. Laboratory data						
a. Blood glucose (mmol/L)			<2.7	2.7–4.4	>4.4	
b. IgG concentration (g/L)	<2.0	2.0–4.0	4.1–8.0		>8.0	
c. Arterial oxygen tension (Torr)		<40	40–50	51–70	>70	
d. Metabolic acidosis (base excess < 0)				Present	Absent	
Total points for this foal						

To calculate the sepsis score, assign foal a score corresponding to the historical physical examination and laboratory data included in the table. A score of 11 or less predicts the absence of sepsis correctly in 88% of cases, whereas a score of 12 or higher predicts sepsis correctly in 93% of cases. For foals less than 12 hours of age that have nursed or received colostrum, assign a value of 2 for the serum immunoglobulin score. If the foal has not nursed, assign a value of 4.

will be low from the transfer into the mammary gland.

Plasma is often incorporated into the therapeutic regimen in foals, both for its immunoglobulin content and for its effect on blood volume and osmotic pressure. Stored plasma can be used. A dose of 20 mL plasma/kg body weight given slowly intravenously is often used, but significantly higher doses are required to elevate circulating immunoglobulins by an appreciable amount. Blood may be collected, the red blood cells allowed to settle, and the plasma removed and stored frozen. The donor plasma should be prescreened for compatibility. Lyophilized hyperimmune equine serum as a source of antibodies may also be fed to foals within 4 hours after birth. Good nursing care is also essential.

Further information on treatment is given in the section on critical care for the newborn later in this chapter.

CONTROL

Methods for avoidance of failure of transfer of passive immunity and the principles for prevention of infectious disease in newborn farm animals follow in this chapter. The control of individual diseases is given under specific disease headings elsewhere in this book.

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PRINCIPLES OF CONTROL AND PREVENTION OF NEONATAL INFECTIOUS DISEASES

The four principles of control and prevention of infectious diseases of newborn farm animals are as follows:

- Reduction of risk of acquisition of infection from the environment
- Removal of the newborn from the infectious environment if necessary
- Increasing and maintaining the nonspecific resistance of the newborn
- Increasing the specific resistance of the newborn through the use of vaccines

The application of each of these principles will vary depending on the species, the spectrum of diseases that are common on that farm, the management system, and the success achieved with any particular preventive method used previously.

REDUCTION OF RISK OF ACQUISITION OF INFECTION FROM THE ENVIRONMENT

The animal should be born in an environment that is clean, dry, sheltered, and conducive for the animal to get up after birth, suck the dam, and establish bonding.[1,2] Calving and lambing stalls or grounds, farrowing crates, and foaling stalls should be prepared in advance for parturition. No conventional animal area can be sterilized, but it can be made reasonably clean to minimize the infection rate before colostrum is ingested and during the first few weeks of life when the newborn animal is very susceptible to infectious disease.

With seasonal calving or lambing there can be buildup of infection in the birth area, and animals born later in the season are at greater risk of disease. In these circumstances it may be necessary to move to secondary lambing or calving areas. In northern climates snow may constrict the effective calving area and result in a significant buildup of infection. Buildup of infection pressure must be minimized by a change to a fresh calving/lambing area and by the frequent movement of feed bunks or feed areas. Any system that concentrates large numbers of cattle in a small area increases environmental contamination, and close confinement of heifers and cows around calving time is a known risk factor for calf mortality. With large herds both the cow herd and heifer herd should be broken into as many subgroups as is practical. Extensive systems where cows calve out over large paddocks are optimal, and with more intense systems a group size no larger than 50 has been suggested.

Lambing sheds and calving areas for beef cattle should be kept free of animal traffic during the months preceding the period of

parturition. In dairy herds, maternity pens separate from other housing functions should be provided and cleaned and freshly bedded between calvings. Certainly they should not also be used as hospital pens.

In swine herds, the practice of batch farrowing, with all-in all-out systems of management and disinfection of the farrowing rooms, is essential. Sows should be washed before entry to the farrowing area, and the floor of the farrowing crate should be of the type that minimizes exposure of the piglet to fecal material at birth.

The swabbing of the **navel** with tincture of iodine or chlorhexidine solutions to prevent entry of infection is commonly practiced by some producers and seldom by others. In a heavily contaminated environment it is recommended, although hard evidence supporting the efficacy of this procedure is currently lacking.[1] Severance of the umbilical cord too quickly during the birth of foals can deprive the animal of large quantities of blood, which can lead to neonatal maladjustment syndrome.

When deemed necessary, some **surveillance** should be provided for pregnant animals that are expected to give birth, and assistance provided if necessary. The major objective is to avoid or minimize the adverse effects of a difficult or slow parturition on the newborn and the dam. Physical injuries, hypoxia, and edema of parts of the newborn will reduce the vigor and viability of the newborn and, depending on the circumstances and the environment in which it is born, may lead to disease or even death soon after birth.

When possible, every effort should be made to minimize exposure of the neonate to extremes of temperature (heat, cold, snow). Shelter sheds should be built if necessary.

In beef herds, the practice of purchasing male dairy calves to foster on to cows whose calves have died should be discouraged. If calves are purchased, they should be from a herd whose health status is known to the veterinarian and certainly never through a market. Similarly, colostrum should be obtained from cows within the herd and stored frozen for future use. Colostrum obtained from a different herd presents a biosecurity risk because it can transmit diseases such as bovine enzootic leukemia or Johne's disease. Furthermore, purchased dairy colostrum is commonly second- or third-milking colostrum and of limited immunologic value. The use of a commercial colostrum supplement or replacer is possible, although they have significant limitations.

REMOVAL OF THE NEWBORN FROM THE INFECTIOUS ENVIRONMENT

In some cases of high animal population density (e.g., a crowded dairy barn) and in the presence of known disease, it may be necessary to transfer the newborn to a noninfectious environment temporarily or permanently. Adult cows shedding enteric pathogens are a risk for calf infection. Thus dairy calves are often removed from the dam at birth and placed in individual pens inside or outdoors in hutches and reared in these pens separately from the main herd. This reduces the severity of neonatal diarrhea and pneumonia and risk for mortality compared with calves allowed to remain with the dam. **Individual housing** in hutches is preferred because this avoids navel sucking and other methods of direct-contact transmission of disease. Humans entering these hutches should also practice interhutch hygiene. The prevalence of disease is higher in enclosed artificially heated barns than in hutches. However, despite the well-established value of individual rearing of calves, animal welfare regulations in several countries require that there be visual and tactile contact between calves. The removal of the cow–calf pair from the main calving grounds to a "nursery pasture" after the cow–calf relationship (neonatal bond) is well established, at 2 to 3 days of age, has proved to be a successful management practice in beef herds. This system moves the newborn calf away from the main calving ground, which may be heavily contaminated because of limited space. It necessitates that the producer must plan the location of the calving grounds and nursery pastures well in advance of calving time. Calves that develop diarrhea in the calving grounds or nursery pasture are removed with their dams to a **"hospital pasture"** during treatment and convalescence. The all-in all-out principle of successive population and depopulation of farrowing quarters and calf barns is an effective method of maintaining a low level of contamination pressure for the neonate.

INCREASING THE NONSPECIFIC RESISTANCE OF THE NEWBORN

Following a successful birth, the next important method of preventing neonatal disease is to ensure that the newborn ingests colostrum as soon as possible. With natural sucking the amount of colostrum ingested by the neonate will depend on the amount available, the vigor of the animal, the acceptance by the dam, and the management system used, which may encourage or discourage the ingestion of liberal quantities of colostrum. Beef cows that calve at a condition score lower than 4 (out of 10) are at higher risk of having calves that develop failure of transfer of passive immunity, and the ideal condition score at calving is 5 to 6.

The method of colostrum delivery that is needed to optimize transfer of passive immunity to the dairy calf will vary with the breed of cow, the management level of the farm, and the priority given to calf health. Owner acceptance of alternate feeding systems to natural sucking also is a consideration. The success of the farm policy for the feeding of colostrum is easily monitored by one of the tests described earlier, as is the effect of an intervention strategy.

Newborn male dairy calves are commonly assembled and transported to market or to calf-rearing units within a few days of birth. Studies have repeatedly shown high rates of FTPI in this class of calf. The high rates occur either because the original owner does not bother to feed colostrum to the calf, knowing it is to be sold, or because calves are purchased off the farm before colostrum feeding is completed. The effects of the transportation can have a further deleterious effect on the defense mechanism of the calves, and they are at high risk of disease.

Calf-rearing units should preferably purchase calves directly from a farm with an established policy of feeding colostrum before the calf leaves the farm, and every effort should be made to reduce the stress of transportation by providing adequate bedding, avoiding long distances without a break, and attempting to transport only calves that are healthy. In some countries there is now legislation requiring the feeding of colostrum and limiting the transport of newborn calves.

The honesty of the stated farm colostrum feeding policy can be monitored by testing the calves for their immunoglobulin concentration in serum. Where this is not possible and market calves must be used, the entry immunoglobulin concentration should be tested; the incidence of infectious disease in low-testing calves will be high unless hygiene, housing, ventilation, management and nutrition are excellent. The entry immunoglobulin concentration of calves entering veal or other calf-rearing units is a prime determinant of subsequent health and performance. The "alert" cut-point can be established for an individual farm by monitoring of individual immunoglobulin concentrations and subsequent calf fate.

Following the successful ingestion of colostrum and establishment of the neonatal bond, emphasis can then be given to provision, if necessary, of any special nutritional and housing requirements. Newborn piglets need supplemental heat, and attention must be given to the special problems of intensive pig husbandry. Orphan and weak piglets can now be reared successfully under normal farm conditions with the use of milk replacers containing added porcine immunoglobulins. Heat is often provided to lambs for the first day in pen lambing systems.

Milk replacers for the newborn must contain high-quality ingredients. Calves younger than 3 weeks are less able to digest nonmilk proteins, and the fats best used by the calf are high-quality animal source fats and slightly unsaturated vegetable oils. A 22% crude protein is recommended for milk

replacers comprised only of milk proteins and 24% to 26% in replacers that contain nonmilk protein sources. The level of fat should be at least 15%; higher fat concentration will provide additional energy, which may be required in colder climates. Feeding utensils must be cleaned and disinfected between each feeding if disease transmission is to be minimized.

With animals at pasture, the mustering and close contact associated with management procedures such as castration and docking pose a risk for disease transmission. These procedures should be performed in yards prepared for the purpose—preferably temporary yards erected for this sole purpose in a clean area.

INCREASING THE SPECIFIC RESISTANCE OF THE NEWBORN

The specific resistance of the newborn to infectious disease may be enhanced by vaccination of the dam during pregnancy to stimulate the production of specific antibodies that are concentrated in the colostrum and transferred to the newborn after birth. Vaccination of the dam can provide protection for the neonate against enteric and respiratory disease. Details are given under the specific disease headings in this text. The vaccination of the late fetus in utero stimulates the production of antibody but its practical application has yet to be determined.

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COLIBACILLOSIS OF NEWBORN CALVES, PIGLETS, LAMBS, KIDS, AND FOALS

SYNOPSIS

Etiology Pathogenic serotypes of *Escherichia coli:* septicemic, enterotoxigenic (ETEC); enteropathogenic (EPEC); enterohemorrhagic (EHEC), also referred to as verocytotoxigenic (VTEC) or Shiga-toxin-producing (STEC); and necrotoxigenic *E. coli* (NTEC).

Epidemiology Affects newborn calves, piglets, lambs, and goat kids. Risk factors include colostrum deprivation, overcrowding, adverse climatic conditions, and inferior milk replacers. Prevalence of ETEC varies between herds. EHEC (O157:H7) in cattle is not normally associated with clinical disease, but it presents a major zoonotic concern.

Signs Weakness and collapse (septicemia), diarrhea, and dehydration; complications such as meningitis or polyarthritis.

Clinical pathology Isolation of organism from feces or blood; hematology and serum biochemistry to evaluate inflammation and acid–base and electrolyte imbalance.

Lesions Septicemic lesions, dehydration, enteritis.

Diagnostic confirmation Culture of organism and serotyping.

Treatment Antimicrobials, antiinflammatory drugs, fluid and electrolyte therapy.

Control Reduce infection pressure on neonates. Ensure adequate transfer of passive immunity, and vaccinate pregnant dams to induce specific colostrum antibody. Minimize stressors and their effect on neonates.

ETIOLOGY

Colibacillosis is associated with pathogenic serotypes of *E. coli*. For the most part, *E. coli* is a group of harmless bacteria that serve as indicator organisms for fecal contamination and breaches in hygiene. However, several strains have acquired virulence factors, turning them into potentially dangerous pathogens.[1] The prevalence of the different pathogenic serotypes of *E. coli* in farm animals has remained relatively constant for many years. Certain serotypes cause diarrhea and others cause septicemia. Serotypes include the following:

- **Enterotoxigenic *E. coli* (ETEC)** is the most common enteropathogen that causes diarrhea in newborn farm animals. The bacteria cause diarrhea by adhering to enterocytes, colonizing the intestinal mucosa, and **producing enterotoxins**. Enterotoxins cause hypersecretion of electrolytes and water into the small intestine without causing significant morphologic damage or invading tissue.[2]
- **Enteropathogenic *E. coli* (EPEC)** are the **"attaching and effacing"** strains that colonize the small intestine, where they attach tightly to the epithelial cells of the villus and cause typical **attaching and effacing lesions**. They do not produce toxins and seldom invade the intestinal mucosa.
- **Enterohemorrhagic *E. coli* (EHEC)** also cause attaching and effacing lesions and are among the *E. coli* strains capable of producing toxins similar to the one produced by *Shigella dysenteriae* type I. They are therefore also referred to as **Shiga-toxin-producing *E. coli* (STEC).** Because Shiga toxins are detected with the Vero cell-toxicity test, STEC are also known as **verotoxin or verocytotoxin-producing *E. coli* (VTEC).** Shiga toxins may cause anything from mild diarrhea to severe hemorrhagic colitis. In humans EHEC is responsible for the highly fatal hemolytic–uremic syndrome in children.[3] **EHEC are highly prevalent in cattle** but in general do not cause clinical disease in this species, although some Shiga-toxin-producing *E. coli* have been associated with diarrhea in calves. Cattle are the main reservoir of ***E. coli*** O157:H7, one of the important EHEC strains, causing a broad range of clinical disease in humans (see the section on enterohemorrhagic *E. coli* in farm animals and zoonotic implications). Shiga-toxin-producing *E. coli* strains have been associated with edema disease in swine.[2]
- **Necrotoxigenic *E. coli* (NTEC)** strains produce cytotoxic necrotizing factor (CNF)1 or 2. NTEC2 isolates are restricted to ruminants, particularly calves and lambs with diarrhea and septicemia.
- **Septicemic *E. coli*** strains of serogroup 078 are invasive and cause septicemia in calves, piglets, and lambs. Their powerful endotoxins cause endotoxic shock, with a high case fatality rate.

EPIDEMIOLOGY

Occurrence and Prevalence of Infection

The prevalence of colibacillosis has increased in recent years. There are several possible reasons for this, including size of herds, shortage of qualified labor, automated livestock-rearing systems, and increased population density.

Colibacillosis occurs most commonly in newborn farm animals and is a significant cause of economic loss in raising livestock. It is a complex disease in which several different risk factors interact with certain pathogens, resulting in the disease. There are at least two different types of the disease: **enteric colibacillosis** is characterized by varying degrees of diarrhea, dehydration, acidosis, and death in a few days if not treated; **coliform septicemia** is characterized by severe illness and rapid death within hours.

Cattle and Calves

The infection prevalence of **enterohemorrhagic *E. coli***, particularly the *E. coli* O157:H7 strain, has been studied extensively because of concerns with beef and raw milk as source

of foodborne disease in humans. In the United States *E. coli* O157:H7 infection prevalence rates based on positive fecal samples were between 0.2% and 8.4% for cows, 1.6% and 3.0% for heifers, and 0.4% to 40% for calves. Infection prevalence rates reported from Canada, Italy, Japan, and the United Kingdom were 0.3% to 16.1% for cows, 10.0% to 14.1% for heifers, and 1.7% to 48.8% for calves.[4] These numbers underscore the obvious effect of animal age on the epidemiology of infection with *E. coli O157:57*. The **considerable prevalence of this EHEC strain** in cattle has little impact on animal health because EHEC infection in this species is normally not associated with clinical disease, but it presents a **serious public health concern**.

The prevalence of **enterotoxigenic *E. coli*** (ETEC) in diarrheic calves varies widely geographically, between herds, and depending on the age of the animals. The prevalence can be as high as 50% to 60% in diarrheic calves under 3 days of age and only 5% to 10% in diarrheic calves 8 days of age. In some countries the prevalence is only 5% to 8% in diarrheic calves under 3 days of age. Thus **enterotoxigenic colibacillosis is a major cause of diarrhea in calves less than 3 days of age** and is not associated with outbreaks of diarrhea in calves older than 3 days. ETEC infection in calves older than 2 to 3 days will in most cases be associated with a viral infection. The prevalence of ETEC infection is very low or nil in clinically normal calves in herds that have not had a problem with diarrhea. In some beef herds affected with diarrhea in young calves there may be little evidence of infection with enterotoxigenic *E. coli,* and other factors need to be examined.

Piglets

The prevalence of ETEC in diarrheic piglets varies geographically and with herds. In some areas the F5 (K99) pilus was found more frequently than F4 (K88) or F6 (987P), whereas in other regions the F4 pilus is more common. The F4 and F18 pilus adhesins are most commonly associated with postweaning diarrhea of pigs.

Morbidity and Mortality Rates

Calves

In dairy calves raised under intensive and poorly managed conditions the morbidity rate of infection with ETEC may reach 75%, but it is usually about 30%. Case fatality rates vary from 10% to 50% depending on the level of clinical management.

In beef calves the morbidity rates vary from 10% to 50% and the case fatality rates from 5% to 25% or even higher in some years. The population mortality rate in both beef and dairy calves can vary from a low of 3% in well-managed herds to a high of 60% in problem herds in certain years.

Piglets

In piglets the morbidity rate of preweaning diarrhea varies widely between herds, but it averages about 6% of litters, mostly in the first week of life. The morbidity rates increase with increased litter size and decrease with increasing parity of the sow. Losses as a result of stillbirths, traumatic injuries, starvation, and undersize at birth account for a much greater combined total preweaning loss, but colibacillosis accounts for approximately 50% of the gastroenteropathies encountered during the preweaning period.

Postweaning diarrhea (PWD) occurring in the 2 weeks following weaning is one of the economically most important diarrheal diseases in piglets in which colibacillosis plays an important etiologic role.[5] ETEC associated PWD commonly occurs in the immediate postweaning period. Outbreaks can occur suddenly, with mortality rates of 50% and higher. Affected animals can die acutely or show profuse diarrhea for up to 4 days. In uncomplicated cases mortality rates rarely exceed 10%.[5] Postweaning diarrhea of pigs is covered in detail under this heading.

Risk Factors

Several risk factors influence the occurrence of the disease, each one of which must be considered, evaluated, and modified or removed if necessary when investigating the cause of an outbreak so that effective clinical management and control of the disease may be achieved.

Animal Risk Factors

Animal Species

The pathogenesis of colibacillosis involves a number of host factors, of which the presence of specific receptors for adhesins and enterotoxins is probably among the most important.[6] Clinical disease associated with *E. coli* infection is largely dependent on the presence of specific receptors that usually only occur in one or few animal species. because of this receptor specificity of adhesins and enterotoxins, **ETEC strains have considerable species specificity**.[7]

Age and Birth Weight

Diarrhea associated with ETEC occurs in **calves** mainly during the first few days of life, rarely in older calves, and never in adults. Epidemiologic studies of both beef and dairy calves indicate that more than 80% of clinical cases associated with ETEC F5 (K99) occur in calves younger than 4 days of age. The ability of the F5 ETEC to adhere to the small intestinal epithelium of calves decreases continuously from 12 hours of age to 2 weeks of age.[8] The mechanism of this age-related resistance is not well understood, but it may be related to development of resistance to colonization of the small intestine as the calf becomes older. This could be associated with the replacement of villous epithelial cells that occurs in the first few days after birth.

The disease is more common in **piglets** born from gilts than from sows, which suggests that immunity develops with developing age in the sow and is transferred to the piglets. In a survey of approximately 4400 litters of piglets over a period of 4 years in a large piggery, 64% of the litters were treated for diarrhea before weaning, and piglets born to sows under parity 2 were 1.7 times more likely to develop diarrhea before weaning than litters born to sows over parity 3. The susceptibility or resistance to *E. coli* diarrhea in piglets has an inherited basis. The cell surface receptor for the F4 (K88) antigen is inherited in a simple mendelian way, with adherence (*S*) dominant over nonadherence (*s*). Homozygous dominants (*SS*) and heterozygotes (*Ss*) possess the receptor and are susceptible, whereas in the homozygous recessive (*ss*) the receptor is absent and the pigs are resistant. The highest incidence of diarrhea occurs in susceptible progeny born from resistant dams and sired by susceptible sires. Most if not all pigs have intestinal receptors for F5 ($K99^+$) pili and an inheritance pattern similar to F4 (K88) receptors does not exist for F5 receptors.

Immunity and Colostrum

Newborn farm animals are agammaglobulinemic and must ingest colostrum and absorb colostral immunoglobulin within hours of birth to obtain protection against septicemic and enteric colibacillosis. The transfer of immunoglobulin from the dam to the neonate is termed *transfer of passive immunity*. **Failure of transfer of passive immunity** predisposes the neonate to development of infectious diseases (see also the section "Failure of Transfer of Passive Immunity").

Transfer of maternal immunoglobulin to calves depends on three successive processes:

- Formation of colostrum with a high concentration of immunoglobulin by the dam
- Ingestion of an adequate volume of colostrum by the calf
- Efficient absorption of colostral immunoglobulin by the calf

Colostral immunoglobulin is absorbed for up to 24 hours after birth in calves and up to 48 hours in piglets. However, in calves the maximum efficiency of absorption occurs during the first 6 to 12 hours after birth and decreases rapidly from 12 to 24 hours after birth. Following absorption, transfer to the intestinal lumen is a major means of IgG clearance in calves, and this transfer results in antigen-binding antibody in the intestinal lumen. Both blood-derived antibody and lactogenic antibody are significant sources of passive antibodies in the intestinal lumen of the neonatal calf. Maintenance of high concentrations of

milk-derived antibodies in the small intestinal lumen may require more than twice-a-day feedings because antibodies derived from a milk diet are predominantly cleared from the intestinal lumen by 12 hours after feeding. Transfer of passively acquired antibodies from the circulation to the small intestinal lumen is therefore a reasonable hypothesis to explain the strong association between high serum passive immunoglobulin concentrations and reduced morbidity in neonatal calves.

Newborn dairy calves should ingest 80 to 100 g of colostral IgG, and ideally up to 150 g, within a few hours after birth to achieve serum immunoglobulin of 1000 mg/dL.

Environmental and Management Risk Factors

Meteorologic Influences

Although few epidemiologic data are available to support the claim, many veterinarians have observed a relationship between adverse climatic conditions and colibacillosis in both calves and piglets. During inclement weather, such as a snowstorm, a common practice in beef herds is to confine the calving cows in a small area, where they can be fed and watered more easily. The overcrowding is commonly followed by an outbreak of acute calf diarrhea. There is evidence that cold, wet, and windy weather during the winter months and hot, dry weather during the summer months have a significant effect on the incidence of dairy calf mortality.

The risk factors for mortality from diarrhea in beef calves in Alberta, Canada, have been examined. The odds of mortality were increased when the cows and heifers were wintered on the same grounds, when the herd was wintered and calved on the same grounds, and if the cows and heifers were calved on the same grounds. The morbidity and mortality rates from diarrhea during the first 30 days of life increased with an increasing percentage of heifers calving in the herd. Heifers are commonly more closely confined during the calving season for more effective observation and assistance at parturition. This may lead to increased contamination of the environment and the abdominal wall and udder of the heifers. Additional factors in heifers include a higher incidence of dystocia and maternal misbehavior and lower volume and quality of colostrum, all of which can result in weak calves that may not acquire sufficient colostral immunity.

Nutrition and Feeding Methods

Dairy calves fed milk substitutes may be more susceptible to acute undifferentiated diarrhea, some of which may be a result of enteric colibacillosis, compared with those fed cows' whole milk. Extreme heat treatment of the liquid skim milk in the processing of dried skim milk for use as milk substitutes for calves results in denaturation of the whey protein, which interferes with digestibility of the nutrients and causes destruction of any lactoglobulins that are present and may have a protective effect in the young calf.

Irregular feeding practices resulting in dietetic diarrhea may contribute to a higher incidence of enteric colibacillosis in calves. The person feeding and caring for the calves is an important factor influencing calf mortality a result of diarrhea. Although it is generally thought that general or specific nutritional deficiencies, such as a lack of energy, protein, or vitamin A, in the maternal diet predispose to colibacillosis, particularly in calves and piglets, there is no direct evidence that specific nutritional deficiencies are risk factors. However, they probably are, at least in indirect ways, for example, by having an effect on the amount of colostrum available at the first milking after parturition in first-calf heifers underfed during pregnancy.

Standard of Housing and Hygiene

Housing and hygienic practices are probably the most important environmental risk factors influencing the incidence of colibacillosis in calves and piglets, but they have received the least amount of research effort compared with other aspects, for example, control of the disease through vaccination. As the size of herds has increased, and as livestock production has become more intensified, the quality of hygiene and sanitation, particularly in housed animals, has assumed major importance. The disease is much less common when calves are run at pasture or are individually tethered, or penned, on grass.

Source of the Organism and Its Ecology and Transmission

Ingestion is the most likely portal of infection in calves, piglets, and lambs, although infection via the umbilical vessels and nasopharyngeal mucosa can occur. It has been suggested that certain serotypes of *E. coli* may enter by the latter route and lead to the development of meningitis.

In most species, it is assumed that the primary source of the infection is the feces of infected animals, including the healthy dams and neonates, and diarrheic newborn animals, which act as multipliers of the organisms. In some cases, the organism may be cultured from the vagina or uterus of sows whose litters become affected. In pig herds the total number of organisms on each sow is highest in the farrowing barn, decreases when the sow is returned to the breeding barn, and is lowest when the sow is in the gestation barn.

Calves acquire the infection from contaminated bedding and calf pails, dirty calf pens, nearby diarrheic calves, overcrowded calving grounds, and the skin of the perineum and udder of the cow. The organism is spread within a herd through the feces of infected animals and all the inanimate objects that can be contaminated by feces, including bedding, pails, boots, tools, clothing, and feed and water supplies. The organism is one of the first encountered by newborn farm animals, usually within minutes after birth. In cattle, the tonsil can be a reservoir for STEC in healthy animals. It is possible that virulent *E. coli* can be present and may be transferred to calves when they are licked by their dams at birth. The high population density of animals that occurs in overcrowded calving grounds in beef herds and heavily used calving pens in dairy herds and the continuous successive use of farrowing crates without a break for cleanup contribute to a large dynamic population of *E. coli.* The population of bacteria in an animal barn will continue to increase with the length of time the barn is occupied by animals without depopulation, clean-out, disinfection, and a period of vacancy. In some countries where lambing must be done in buildings to avoid exposure to cold weather, the lambing sheds may become heavily contaminated within a few weeks, resulting in outbreaks of septicemic and enteric colibacillosis.

Infected animals are the main reservoir for ETEC, and their feces are the major source of environmental contamination with the bacteria. Passage of the *E. coli* through animals causes a "multiplier effect"; each infected animal excretes many more bacteria than it originally ingested. Diarrheic calves are the most extreme multipliers because they often pass 1 L or more of liquid feces containing 10^{10}/g ETEC within 12 hours, and recovered calves can continue to shed bacteria for several months.

Normal calves and adult cows can serve as reservoirs of infection, and the bacteria can persist in a herd by circulating through animals of all ages. Carrier animals introduced to an uninfected herd are thought to be one of the main causes of natural outbreaks. The duration and amount of shedding probably depend on the degree of confinement, resulting population density, herd immunity, environmental conditions, and perhaps the serotype of the organism.

Pathogen Risk Factors

Virulence Factors of E. coli

Virulence factors of *E. coli* include *pili (fimbriae), enterotoxins (exotoxins), endotoxins,* and *capsules.* The adhesins in the pili of ETEC allow them to adhere to intestinal villous epithelial cells and prevent peristaltic elimination by the gut and to produce enterotoxins.

The virulence factors are relevant to vaccine efficacy. The species-specific adhesin antigens must be identified and incorporated into vaccines, which are given to pregnant females in an attempt to stimulate the production of specific antibody in the

colostrum, which will provide protection against enterotoxigenic colibacillosis. An essential element of vaccine development is the detection of common fimbrial antigens occurring among most pathogenic isolates and able to induce antibodies that block bacterial adhesion. The great diversity of potential pathogenic serotypes encountered in colisepticemia and the failure of serotype-specific antibody to cross-protect against a heterologous challenge in experimental infection have made it difficult to develop vaccines against septicemic colibacillosis.

The major virulence factors of ETEC in calves are the F5 (K99) adhesin antigen and the heat-stable enterotoxin (ST). The colonization in the small intestine of calves by F5 ETEC appears to be site specific, having a predilection for the ileum. Some serogroups also elaborate the F41 adhesin to the F5. Other surface-adhesive antigens, such as Att 25 and F17, have been identified on bovine enteropathogenic and septicemic *E. coli*. The F17a-positive ETEC strains are no longer isolated from diarrheic calves in some countries. It is postulated that the use of a vaccine including O101, K32, and H9 antigens in addition to F5 explains the strongly reduced incidence of the O101:K32:H9, F5 *E. coli* clone. A F4-related fimbrial antigen occurs on some enterotoxigenic and septicemic strains.

Enterotoxins are plasmid-regulated secreted peptides of ETEC bacteria that affect the intestinal epithelium. Two types of enterotoxins are differentiated, large-molecular-weight (88 kDA) heat-labile enterotoxins (LT) and small-molecular-weight heat-stable enterotoxins (ST).[7] LT enterotoxins are predominantly produced by human and porcine ETEC strains, whereas ST enterotoxins are produced by human, porcine, and bovine ETEC strains. The heat-stable enterotoxin from bovine ETEC has been purified and characterized. There is evidence of a form of ST enterotoxin that is common to bovine, porcine, and human strains of ETEC.

Most strains of **septicemic *E. coli*** belong to certain serogroups with virulence properties that enable them to resist the defense mechanisms that would normally eliminate other *E. coli*. **Septicemic strains produce endotoxin**, which results in shock and rapid death, usually in calves that are less than 5 days of age and with FTPI. Isolates of *E. coli* from the blood of critically ill bacteremic calves on a calf-rearing farm in California constituted a heterogeneous group and were found to be aerobactin positive and often resistant to the bactericidal effects of serum. The relative importance of individual serogroups varies between countries. However, it has been established that typeable isolates of *E. coli* from septic calves belong to a relatively small number of serogroups.[9] Strains commonly isolated from calves with septicemia belong to serogroups O78 and O15.[9,10]

Enterohemorrhagic *E. coli* (EHEC) and Shiga-toxin-producing *E. coli* (STEC) are recognized in humans and animals with increased frequency and constitute a major zoonotic concern (see the discussion of enterohemorrhagic *E. coli* in farm animals and zoonotic implications). These organisms are members of O111, O1O3, O5, and O26 serogroups, and none produces enterotoxin, nor do they possess the F5 pili. They produce the potent Shiga toxins or verotoxins SLT1 and SLT2; and some strains, the **attaching and effacing** *E. coli* (**AEEC**), attach to and efface the microvilli of the enterocytes, causing diarrhea and dysentery as a result of hemorrhagic colitis in calves 2 to 5 weeks of age. The effacing (*eae*) gene and the gene coding for the Shiga toxin 1 (*SLT1*) are associated with most isolates of AEEC in cattle. They have been isolated from both diarrheic and healthy sheep and goats.

A study of the onset and subsequent pattern of shedding of STEC O26, O103, O111, O145, and O157 in a cohort of beef calves on a mixed cattle and sheep farm in Scotland found that O26 was shed by 94% of the calves and that 90% of the O26 isolates carried the *vtx1*, *eae*, and *ehl* genes. *E. coli* O103 was the second most commonly shed serogroup of the tested calves, and the pattern of shedding was sporadic and random. There was an absence of shedding of *E. coli* O111, and the prevalence of shedding of O145 was low. Although some shedding of O157 occurred, shedding in calves was sporadic and infrequent. For O26, O103, and O157, there was no association between shedding by calves and shedding by dams within 1 week of birth. For O26 and O103, there was no association between shedding and diarrhea and no significant change in shedding following housing. In a sample of Australian dairy farms, calves as young as 48 to 72 hours had evidence of fecal excretion of STEC, indicating that dairy cattle are exposed to STEC from birth. Calves at weaning are most likely to shed STEC O26 or *E. coli* O157, similar to the prevalence surveys in the northern hemispheres.

Naturally occurring cases of attaching and effacing lesions of the intestines in calves with diarrhea and dysentery and infected with *E. coli* O126:H11, the predominant *STEC* strain in humans, have been described in the United Kingdom. STEC and *eae*-positive non-STEC have been isolated from diarrheic dairy calves 1 to 30 days of age.

E. coli O157 has been isolated from neonatal calves and has been implicated as a cause of diarrhea in calves. The isolates carried various virulence genes, such as *Ehly*, *eae*, *stx1*, and *stx2*. The *Ehly* gene may be a virulence marker for bovine enterohemorrhagic *E. coli* O157 strains. Similar findings have been reported in dairy cattle herds in Brazil. Strains of *E. coli* possessing a subtype beta intimin, normally found in human enteropathogenic *E. coli*, have been found in diarrheic calves in Brazil.

Non-O157 STEC have been isolated from diarrheic calves in Argentina, and the serotypes carried virulence traits associated with increased pathogenicity in humans and cattle. Severe clinical syndromes associated with non-O157 STEC are common in children under 4 years of age and may be associated with diarrheic calves, which shed highly virulent STEC strains and could act as a reservoir and contamination source in these areas.

E. coli O116, a serogroup previously associated with cases of hemolytic–uremic syndrome in humans, has been associated with an outbreak of diarrhea and dysentery in 1- to 16-week-old calves in India. *E. coli* O103:H2, an STEC strain causing disease in humans, has been isolated from calves with dysentery and from a sheep in Australia.

Necrotoxigenic *E. coli* (NTEC), which produce **cytotoxic necrotizing factor (CNF)**, have been isolated from cattle in Northern Ireland and Spain and from diarrheic piglets in England. NTEC1 strains from cattle, pigs, and humans can belong to the same serogroups/biogroups, carry genes coding for adhesions belonging to the same families, and possess other identical virulence-associated properties, and they therefore do not exclude the possibility of cross-infection between humans and farm animals in some cases. In Spain NTEC were detected by tissue culture and PCR in 15.8% of diarrheic dairy calves from 1 to 90 days of age; the majority were NTEC producing CNF2, and the risk increased with age. There was also a strong association between CNF2 and F17 fimbriae. The NTEC, with their associated adhesins and toxins, were present in diarrheic and septicemic calves as early as 1958, and their prevalence seems to be increasing. Their role in causing disease needs further examination.

Most ETEC from **neonatal pigs** belong to the so-called "classical serogroups": O8:K87, O45, O138:K81, O141:K85, O147:K89, O149:K91, and O157:KXVX17. Strains of these serogroups usually express and produce F4 (K88), F5 (K99), F6 (987P), F18 and F41 pilus antigens. With the exception of F18, these pilus antigens mediate adhesion of *E. coli* to ileal villi in neonates, causing profuse diarrhea in unweaned pigs. The F4 and F5 piliated strains are the most common cause of enteric disease in piglets under 2 weeks of age. ETEC strains that produce F6 pili colonize the small intestines and cause diarrhea in neonatal pigs under 6 days of age, but not older pigs. F18, in contrast, is not associated with neonatal colibacillosis in piglets, but together with F4 is the most common adhesin associated with postweaning colibacillosis. There are also some ETEC strains that produce none of the antigens mentioned previously.

F4 produces heat-labile enterotoxin (LT), F5 and F6 do not produce LT, and all three

types produce heat-stable enterotoxin STa in infant mice. Some isolates produce neither LT nor STa but produce enterotoxin in ligated intestinal loops of pigs (STb). Other "nonclassical" strains colonize the small intestine to a certain extent, do not strongly adhere to the intestinal epithelium, and produce enterotoxin and diarrhea in neonatal piglets.

The porcine ETEC strains that induce diarrhea in piglets less than 2 weeks of age but not in older pigs are designated class 2, whereas those strains that induce diarrhea in older pigs are class 1 ETEC. The bovine ETEC strains have several features in common with the porcine class 2 organisms, which include the possession of the 0 antigens 8, 9, 20, or 101; characterization as mucoid colonies; possession of F5 pili; and production of heat-stable enterotoxin. Most ETEC strains of pigs belong to a restricted number of serogroups.

Lambs

Enterotoxigenic strains of *E. coli* can be isolated from the feces of approximately 35% of diarrheic lambs. ETEC strains have also been isolated from the blood of a small percentage of diarrheic lambs. F5 (K99) piliated *E. coli* are associated with outbreaks of diarrhea in lambs under a few days of age. F17 fimbriae *E. coli* have been isolated from diarrheic lambs and kids, but none of the isolates produced any of the toxins normally associated with ETEC strains. Attaching and effacing *E. coli* negative for Shiga toxin but positive for *eae* have been isolated from goat kids affected with severe diarrhea, with a high case fatality rate.

Zoonotic Implications of *E. coli*

Cattle are a major source of EHEC strain O157:H7, which is associated with foodborne disease in humans. (See "Enterohemorrhagic *Escherichia coli* in Farm Animals and Zoonotic Implications.")

PATHOGENESIS

The factors important in understanding the pathogenesis of colibacillosis are the affected species, the age and the immune status of the animal, and the virulence factors of the strain of *E. coli,* particularly its capacity to invade tissues and produce septicemia or to produce an enterotoxin. Diarrhea, dehydration, metabolic acidosis, bacteremia, and septicemia are the major pathogenetic events in the various forms of colibacillosis.

Septicemic Colibacillosis (Coliform Septicemia)

Septicemic colibacillosis occurs in all species as a result of invasive strains of *E. coli* invading the tissues and systemic circulation via the intestinal lumen, nasopharyngeal mucosa, and tonsillar crypts, or umbilical vessels. The intestinal permeability to macromolecules in the newborn piglet may predispose to the invasion of septicemia-inducing *E. coli.* These strains are able to invade extraintestinal tissues, to resist the bactericidal effect of complement in blood, to survive and multiply in body fluids, to escape phagocytosis and intracellular killing by phagocytes, and to induce tissue damage by the release of cytotoxins. Calves and piglets that are deficient in colostral immunoglobulins are highly susceptible to septicemia. Colostrum provides protection against colisepticemia, but it may not prevent diarrhea associated with *E. coli.* Also, colostrum-fed calves are much more resistant to endotoxin than colostrum-deprived calves. Calves, piglets, and lambs that have normal levels of serum immunoglobulins are generally protected from septicemia. The clinical findings and lesions in septicemic colibacillosis are attributable to the effects of endotoxin, which causes shock. The general effects of endotoxin in cattle include hypothermia, decreased systemic blood pressure, tachycardia and decreased cardiac output, changes in WBC counts, alterations in blood coagulation, hyperglycemia followed by hypoglycemia, and depletion of liver glycogen. Animals that recover from septicemia may later develop lesions as a result of local infection of other organs at varying periods of time. Arthritis is a common associated finding in calves, foals, and lambs. Meningitis is common in calves and piglets. Polyserositis as a result of *E. coli* has been recorded in pigs.

Enteric Colibacillosis

Enterotoxigenic Colibacillosis

Enterotoxigenic strains of *E. coli* (ETEC) colonize and proliferate in the upper small intestine and produce enterotoxins, which cause an increase in net secretion of fluid and electrolytes into the gut lumen. The adhesion of *E. coli* to the intestinal epithelial cells is mediated by bacterial pili. The enterotoxigenic form of colibacillosis occurs most commonly in calves and piglets and less commonly in lambs and kids.

The factors that allow or control the colonization and proliferation of these strains and their production of enterotoxin are not well understood. The bacterial fimbriae attach to specific receptor sites on villous epithelial cells, following which the bacteria multiply and form microcolonies that cover the surface of the villi. The capsular polysaccharide of *E. coli* may also be involved in adhesion and colonization. The fimbriae of *E. coli* are strongly immunogenic, a factor that is utilized in the production of vaccines. Because the F5 antigen is only expressed at an environmental pH above 6.5, colonization of the mucosa of the small intestinal tract starts in the ileum, where the intraluminal pH is the highest, and progresses proximally from there.[8] Once established in the gut, ETEC strains start producing and secreting a heat-stable enterotoxin. Similar to the expression of F5, production of enterotoxin is pH dependent, with very limited production at an environmental pH below 7.0.[8] Although this does not appear to have been studied specifically, it can be hypothesized that any factor resulting in an increase of the pH in the gut lumen will facilitate the proliferation of the organism; conversely, lowering the pH may reduce the severity of colibacillosis.

Diarrhea, Dehydration, Metabolic Acidosis, and Electrolyte Imbalance

The production of the enterotoxin results in net secretion of fluid and electrolytes from the systemic circulation into the lumen of the intestine, resulting in varying degrees of diarrhea, dehydration, electrolyte imbalances, acidemia, circulatory failure, shock, and death. The hyperkalemia that is observed in a subset of calves with severe dehydration and acidemia has been associated with cardiac arrhythmias, including bradycardia and atrial standstill.

The effect of the enterotoxin on the gut of calves, piglets, and other species is similar to the effect of cholera enterotoxin in humans and takes place through an intact mucosa. Enterotoxin stimulates mucosal adenylcyclase activity, leading to an increase in cyclic adenosine monophosphate (AMP), which increases intestinal chloride secretion. The increased intraluminal chloride content osmotically drags water into the gut to an amount that exceeds the absorptive capacity of the intestinal mucosa, thereby causing diarrhea. The secretion originates primarily in the intestinal crypts, but the villous epithelium also has a secretory function. The mucosal membrane colonized by ETEC remains morphologically intact. The fluids secreted are alkaline and, in comparison to serum, isotonic, low in protein, and high in sodium and bicarbonate ions. Distension of the abdomen of diarrheic calves may occur, which may be associated with fluid distension of the abomasum and the intestines.

When the disease is confined to the intestine, it responds reasonably well to treatment in the early stages. If death occurs, it is a result of acidemia, electrolyte imbalance, and dehydration. The acid–base and electrolyte changes in piglets 1 to 3 days of age infected naturally and experimentally with ETEC reveal severe dehydration, acidemia, and metabolic acidosis.

Severe metabolic changes can occur in calves with diarrhea. If the disease is progressive, acidemia and metabolic acidosis become more severe as lactic acidosis develops, and severe hypoglycemia may occur. If large amounts of fluid are lost, hypovolemia and shock occur.

Historically, conventional wisdom held that **metabolic acidosis** in diarrheic calves is the result of fecal bicarbonate loss and formation of L-lactate as a result of increased anaerobic glycolysis in dehydrated animals

with decreased tissue perfusion. However, accumulation of L-lactate in neonatal diarrheic calves only appears to occur in calves in their first week of life. Because the relationship between L-lactic acid accumulation and the severity of metabolic acidosis could not be confirmed in clinical cases, it was proposed that exogenous acid supply to the organism must be the major contributor to the so-called **anion-gap acidosis** typically observed in diarrheic calves.[12] The anion gap, defined as the sum of the major cations minus the sum of the major anions, is a measure of "unspecified organic and inorganic acids," of which lactic acid forms a considerable part. It was not until the end of last century that **D-lactic acid accumulation** was first identified as a major contributor to elevated anion gaps in diarrheic calves. In the meantime, several studies confirmed that D-lactic but not L-lactic acidosis is a common occurrence in diarrheic calves. Furthermore D-lactic acidosis was identified as a major contributory factor in calves with high anion-gap acidosis.[12] It is currently assumed that D-lactic acidosis is caused by increased intestinal absorption of this compound in diarrheic calves, where malabsorption results in bacterial fermentation of unabsorbed carbohydrates to D-lactate.[12] Recent retrospective studies suggested that the major driving factor of the acidemia of diarrheic calves was an increase in unmeasured anions, of which lactic acid forms a considerable part. The loss of fluid through the intestinal tract with high sodium and low chloride content is likely to contribute to the so-called strong-ion acidosis. The increase of the total plasma protein concentration that is commonly observed with marked dehydration and resulting in a so-called weak-acid acidosis was found to be a minor contributor to acidemia in diarrheic calves.[13]

The severity and nature of the acidosis in diarrheic calves vary with the age of the calf. Younger calves tend to dehydrate more rapidly and severely than older calves, which may be related to the greater incidence of enterotoxigenic colibacillosis in the young age group. The severity of dehydration, hypothermia, and acidemia is associated with the level of obtundation. Accordingly, the degree of deterioration of the patient's demeanor in combination with the age of the calf are used to predict the severity of acidemia; the more severe the acidemia, the greater the depression.

Conventional wisdom posits that neurologic effects such as ataxia, somnolence, or even coma are primarily caused by severe acidemia or metabolic acidosis, but a series of recent studies unequivocally demonstrated that disturbed neurologic function can better be explained by the frequently observed increase in plasma D-lactate concentration than acidemia/metabolic acidosis per se.[14,15] Experimental studies conducted on euhydrated calves showed that neurologic signs similar to the ones observed in severely diarrheic calves can be reproduced by inducing hyper–D-lactatemia without concomitant acidosis. In contrast, experimentally inducing severe hyperchloremic acidosis in calves did not result in noteworthy effects on the demeanor of treated calves.[16,17]

Hyperkalemia in the Diarrheic Calf

Hyperkalemia is the most prominent electrolyte disturbance recognized in dehydrated diarrheic calves that are severely acidemic. It occurs despite significant net losses of potassium into the gut in diarrheic animals. A recent retrospective study conducted on patients of a teaching hospital revealed an incidence of hyperkalemia in diarrheic calves of 34%.[18] The predominant clinical finding associated with hyperkalemia is bradycardia and arrhythmia that can lead to atrial standstill, with fatal outcome. Although the association between hyperkalemia and acidemia is well established, the underlying mechanism is poorly understood.[19] The long-held mechanism responsible for hyperkalemia in diarrheic calves is directly associated with extracellular acidosis and the electrochemical exchange of K^+ for H^+ across the cell membrane, leading to a shift of potassium from the extracellular to the intracellular space in exchange for H^+ that tends to shift into the opposite direction with increasing extracellular H^+ concentrations. Although widely accepted, this proposed mechanism lacks a sound physiochemical basis because a decrease in plasma pH from 7.4 to 7.0 would increase the extracellular H^+ concentration from 0.000,040 mmol/L to 0.000,100 mmol/L. An equimolar exchange of K^+ for H^+ can therefore only account for an increase of the serum potassium concentration of 0.000,06 mmol/L, an effect that not only is not measurable with current laboratory equipment but also is physiologically irrelevant.[19] An alternative mechanism that has been proposed is impaired activity of Na/K-ATPase in states of acidemia, resulting in impaired transport of potassium into the intracellular space.[19] The previously mentioned retrospective study found the occurrence and the degree of hyperkalemia to be more closely associated to the degree of dehydration than to the decrease in venous blood pH or base excess, suggesting that the impaired ability to excrete potassium through the urinary tract may play a more important role than metabolic acidosis/acidemia in the etiology of hyperkalemia in dehydrated calves.[18]

Hypernatremia in the Diarrheic Calf

Hypernatremia is uncommon in diarrheic calves generally suffering from isotonic or mildly hypotonic dehydration. However, incidental cases of hypernatremia have been reported. It is presumed that mixing errors in the preparation of oral electrolyte solutions to treat diarrhea rather than diarrhea itself is the cause. The experimental oral administration of 1 L of electrolyte concentrate containing 2750 mEq sodium found that calves would willingly consume the solution mixed with milk, and developed signs of hypernatremia within 6 hours of administration.

Effect of Colostral Immunoglobulin Status

An adequate level of serum immunoglobulin can protect calves from death as a result of the effects of diarrhea, but not necessarily from diarrhea. The best protection is provided if both the immunoglobulin levels in the serum and the levels in the colostrum and milk during the first week after birth are high. The immunoglobulin subclasses in the plasma of calves that have received sufficient colostrum are IgG, IgM (and IgM is probably the more important of the two for the prevention of septicemia), and IgA. The serum IgG concentrations of calves under 3 weeks of age dying from infectious disease were much lower than those in normal calves. Of the dead calves, 50% had serum IgG levels that were more than 2 standard deviations below the normal mean, and an additional 35% had concentrations greater than 1 standard deviation below the normal mean. In the intestine, no single subclass of immunoglobulin is known to be responsible for protection against the fatal effects of diarrhea. Individually, each immunoglobulin subclass can prevent death from diarrhea even though calves may be affected with varying degrees of diarrhea. In contrast to the situation in the pig, IgA appears to be least effective.

In pigs, IgA becomes the dominant immunoglobulin in sow colostrum after the first few days of lactation, and this is the immunoglobulin that is not absorbed but is retained in, and reaches a high level in, the gut and plays a major role in providing local protection against enteric colibacillosis in piglets. Porcine colostral IgA is more resistant to gastrointestinal proteolytic enzymes than IgG_2 and IgM. On the other hand, IgG is at a peak concentration in colostrum in the first day after parturition, is readily absorbed by the newborn piglet, and is vital in providing protection against septicemia. Lysozyme in sows' milk may assist in the control of the bacterial population in the gut of the unweaned piglet.

Intestinal Mucosa

In general, ETEC exert their effects by the enterotoxin causing hypersecretion through an intact intestinal epithelium. However, the intraluminal exposure of the jejunum of 3-week-old pigs to sterile crude-culture filtrates from strains of *E. coli* known to produce two types of ST will induce microscopic alterations of the villous epithelium. Focal emigration of neutrophils, especially through the epithelium above aggregated lymphatic follicles; stunting of jejunal and

ileal villi; and adherence of bacteria to jejunal and ileal mucosae are the most consistent findings. These changes are useful in making the diagnosis of enterotoxigenic colibacillosis in calves. Although enterotoxigenic strains are considered to be noninvasive, this does not preclude the possibility that invasion into the systemic circulation may occur, resulting in septicemia, or that septicemic strains may not also be present.

Enzyme histochemistry studies of the small intestinal mucosa in experimental infections of calves with rotavirus and ETEC indicate a marked decrease in enzyme activity in dual infections and a lesser decrease in monoinfections. Increased enzyme activity occurred in parts of the intestinal mucosa that were not affected or only slightly affected by the enteropathogens, which may be an adaptation of the mucosa to maintain absorptive function. Lactose digestion is slightly impaired in calves with mild diarrhea. Calves with acute diarrhea are in a catabolic state and respond with a larger increase of plasma glucose concentration to a given amount of absorbed glucose than do healthy calves.

Fat and carbohydrate malabsorption frequently occurs in diarrheic calves over 5 days of age and contributes to the development of D-lactic acidosis, which has been associated with a strong neurotoxic effect that is presumably responsible for the impaired demeanor of diarrheic calves.

Attaching and Effacing Colibacillosis

Attaching and effacing enteropathogenic *E. coli* can cause naturally occurring diarrhea and dysentery in calves at 18 to 21 days. They do not produce enterotoxin but adhere to the surface of the enterocytes of the large intestine. Affected calves pass bright red blood in the diarrheic feces. The lesions in experimentally infected calves are indistinguishable from those produced by some *E. coli* that are enteropathogenic for humans, rabbits, and pigs. The bovine O118:H16 EHEC strain is able to colonize the intestine of newborn calves, inducing diarrhea 24 hours after challenge and producing attaching and effacing lesions in the small and large intestines.

Synergism Between Enteropathogens

Enterotoxigenic colibacillosis occurs naturally and can be reproduced experimentally using ETEC in calves less than 2 days of age but not in calves 1 week of age. Diarrheic calves older than 3 days of age may be infected with enterotoxigenic F5 (K99) *E. coli* and rotavirus. There is evidence that prior or simultaneous infection of the intestine with rotavirus will enable the *E. coli* to colonize in older calves. Thus there may be synergism between rotavirus and ETEC in calves older than 2 days; this may explain the fatal diarrhea that can occur in calves at 1 week of age, which normally would not be fatal with a single infection. The rotavirus may enhance the colonization of *E. coli*.

The simultaneous experimental infection of neonatal gnotobiotic calves at 24 hours of age with rotavirus and ETEC results in a severe diarrheal disease. The same situation occurs in piglets. However, in both species the effect was considered to be additive rather than synergistic.

Summary of Pathogenesis

Septicemic colibacillosis occurs in newborn animals, and FTPI is the major predisposing factor. Enteric colibacillosis occurs in colostrum-fed animals and is associated with the colonization and proliferation of ETEC, which produce enterotoxin and cause varying degrees of diarrhea, acidemia, and dehydration. Although single infections occur commonly, as in piglet diarrhea, and what was previously described as enteric–toxemic colibacillosis in calves, multiple infections with ETEC and viruses and other agents are more common.

CLINICAL FINDINGS

Calves

Coliform Septicemia

Coliform septicemia is most common in calves during the first 4 days of life and is described as the systemic inflammatory response syndrome (SIRS) to an active infectious process.[20] Most affected calves have low levels of serum IgG because of inadequate transfer of colostral immunoglobulin.[21] The illness is peracute, with the course varying from 24 to 96 hours, with a survival rate of less than 12%. Early clinical signs are vague and nonspecific. Affected animals are weak and obtunded, commonly recumbent, and dehydrated; tachycardia is present, and although the temperature may be high initially, it falls rapidly to subnormal levels when the calf becomes weak and moribund. The suck reflex is weak or absent, the oral mucous membranes are dry and cool, and the capillary refill time may be prolonged. Cold extremities, weak peripheral pulse, and prolonged capillary refill time are common. Scleral injection is common. Diarrhea and dysentery may occur but are uncommon.

The involvement of multiple body systems and organs is characteristic of neonatal septicemia, and careful clinical examination is required to detect abnormalities. If a calf survives the septicemic state, clinical evidence of postsepticemic localization may appear in about 1 week. This includes arthritis, meningitis, panophthalmitis, and, less commonly, pneumonia. In a series of 32 cases of meningitis in neonatal calves, the most frequent clinical findings were lethargy, anorexia, recumbency, loss of the suck reflex, stupor, and coma. Opisthotonos, convulsions, tremors, and hyperesthesia were seen less frequently. The case fatality rate was 100% in spite of intensive therapy, and lesions of septicemia were present at necropsy.

Predictors of Septicemia

The early clinical findings of septicemia in neonatal calves are vague and nonspecific and are often indistinguishable from the findings of noninfectious diseases or those of focal infections such as diarrhea. Positive blood cultures are required for a definitive diagnosis of septicemia, but results are not usually available for 48 to 72 hours, and false negatives are common. Laboratory parameters that have been proposed to identify potentially septic calves include hypoglycemia, left shift of neutrophils, and signs of toxicity of neutrophils.[20]

No single laboratory test has emerged as being completely reliable for the early diagnosis of septicemia in farm animal neonates, and therefore scoring systems and predictive models using obtainable historical, clinical, and clinicopathologic data have been developed.[20] The goal of these mathematical models is to identify septicemic neonates early in the course of disease when appropriate therapy would be most likely to result in a favorable outcome. In a study of diarrheic calves under 28 days of age submitted to a referral clinic for treatment, 31% of the calves were septicemic, based on blood culture. Two models to predict septicemia were used. Clinicopathologic variables associated with an increased risk of septicemia were moderate (1.99 to 5.55 mg/dL) and marked (>5.66 mg/dL) increases in serum creatinine (OR 8.63), moderate to marked toxic changes in neutrophils (OR 2.88), and FTPI (IgG concentrations β 800 mg/dL, globulin β 2 g/dL [OR 2.72], and total serum protein β 5 g/dL). The clinical variables associated with an increased risk of septicemia were age under 5 days (OR 2.58), focal infection (OR 2.45), recumbency (OR 2.98), and weak suck reflex (OR 4.10).

Enteric Colibacillosis

Enteric colibacillosis is the most common form of colibacillosis in newborn calves, primarily 3 to 5 days of age. It may occur in calves as early as 1 day of age and only rarely up to 3 weeks. The clinical severity will vary depending on the number and kind of organisms causing the disease. The presence of a single ETEC may cause a state of collapse usually designated as **enteric toxemia**. In this form of the disease the outstanding clinical signs include severe weakness, coma, subnormal temperature, cold and clammy skin, pale mucosae, wetness around the mouth, collapse of superficial veins, slowness and irregularity of the heart, mild convulsive movements, and periodic apnea. Diarrhea is usually not evident, although the abdomen may be slightly distended, and succussion and auscultation may reveal fluid-splashing sounds suggesting a fluid-filled intestine. The prognosis for these calves is poor, and they commonly die 2 to 6 hours after the onset of signs.

In the more common form of the disease in calves, there is diarrhea in which the feces

are profuse and watery to pasty, usually pale yellow to white in color, and occasionally streaked with blood flecks and very foul-smelling. The dry-matter content of the feces is commonly below 10%. Defecation is frequent and effortless, and the tail and perineum are soiled with feces. The temperature is usually normal in the initial stages but becomes subnormal as the disease worsens. Affected calves may or may not suck or drink depending on the degrees of acidosis, dehydration, and weakness. Calves under 8 days of age may be weak, primarily from the effects of rapid and severe dehydration; in calves older than 8 days the acidemia and metabolic acidosis, a considerable part of which is a result of the accumulation of D-lactic acid, tend to be more severe and make a greater contribution to obtundation and weakness. In the early stages of the disease, the abdomen may be slightly distended as a result of distension of fluid-filled intestines, which can be detected by succussion and auscultation of the abdomen. In some of these calves the diarrhea is not yet obvious but is delayed for several hours, when it can become quite profuse. Mildly to moderately affected calves may be diarrheic for a few days and recover spontaneously with or without treatment. However, 15% to 20% of calves with enteric colibacillosis become progressively worse over a period of 3 to 5 days, gradually become more weak, lose the desire to suck, and progressively appear more obviously dehydrated.

Throughout the course of the diarrhea the degree of dehydration will vary from just barely detectable clinically (4% to 6% of body weight [BW]) to up to 10% to 16% of body weight. The degree of dehydration can be estimated by "tenting" the skin of the lateral portion of the cervical region and measuring the time required for the skin fold to return to normal. In calves with 8% dehydration, 5 to 10 seconds will be required for the skin fold to return to normal; in 10% to 12% dehydration, up to 30 seconds will be required. Recession of the eyeball (enophthalmos) is an alternative method validated to reliably estimate the degree of dehydration in diarrheic calves. Slight sinking of the eyeball without an obvious space between the eyeball and the orbit represents 6% to 8% dehydration, moderate separation of the eyeball from the orbit represents 9% to 12% dehydration, and marked separation of the eyeball from the orbit represents over 12% and up to 16% dehydration. A summary of the relationship between degree of dehydration (% BW), depth of enophthalmos (mm), cervical skin tent duration in seconds, and the state of the mucous membranes and extremities in calves with experimentally induced diarrhea is set out in Table 19-12.[1]

Affected calves can lose 10% to 16% of their original body weight during the first 24 to 48 hours of the diarrhea. The hyperkalemia in calves with neonatal diarrhea has been associated with cardiac rate and rhythm abnormalities, including bradycardia and atrial standstill. Herd outbreaks of the disease in beef calves may last for several weeks, during which time almost every calf will be affected within several days after birth.

Veal calf hemorrhagic enteritis is a fatal syndrome of veal calves characterized by anorexia, fever, diarrhea with mucus-containing feces that become bloody in the later stages, and hemorrhagic diathesis on the conjunctivae and mucous membranes of the mouth and nose. The etiology is unknown; the *E. coli* strains isolated from the feces of affected calves produced enterotoxins and Shiga toxins, but their significance is uncertain.

In some calves between 10 and 20 days of age with a history of diarrhea in the previous several days, from which they have recovered, there will be metabolic acidosis without clinical signs of dehydration. Affected calves are depressed, weak, ataxic, and sometimes recumbent, and they appear comatose. Affected calves respond quickly to treatment with intravenous sodium bicarbonate. A similar syndrome occurs in goat kids.

Lambs and Goat Kids

Although some cases manifest enteric signs, and chronic cases may occur, colibacillosis in lambs is commonly septicemic and peracute. Two age groups appear to be susceptible: lambs 1 to 2 days of age and lambs 3 to 8 weeks old. Peracute cases are found dead without premonitory signs. Acute cases show collapse and occasionally signs of acute meningitis manifested by a stiff gait in the early stages, followed by recumbency with hyperesthesia and tetanic convulsions. Chronic cases are usually manifested by arthritis. The disease in goat kids is similar to that in lambs.

Table 19-12 Degree of dehydration in calves with experimentally induced diarrhea

Degree of dehydration (% BW)	Depth of enophthalmos (mm)	Cervical skin-tent duration (s)	Mucous membranes and extremities
0	None	Less than 2	Moist
2	1	3	Dry
4	2	4	Dry
6	3	5	Dry
8	4	6	Cool extremities
10	6	7	Cool extremities
12	7	>8	Cool extremities
>14	>8	>10	White mucous membranes

Piglets

Coliform Septicemia

Coliform septicemia is uncommon but occurs in piglets within 24 to 48 hours of birth. Some are found dead without any premonitory signs. Usually more than one piglet, and sometimes the entire litter, will be affected. Severely affected piglets seen clinically are weak and almost comatose, appear cyanotic, feel cold and clammy, and have a subnormal temperature. Usually there is no diarrhea. The prognosis for these piglets is poor, and most will die in spite of therapy.

Edema disease is unique form of colibacillosis occurring in piglets between a few days after birth to well after weaning. It is caused by Shiga-toxin-producing *E. coli* strains that induce degenerative angiopathy of small arteries and arterioles.

Enterotoxigenic Colibacillosis

Newborn Piglet Diarrhea

Newborn piglet diarrhea, a form of colibacillosis in piglets, occurs from 12 hours of age up to several days of age, with a peak incidence at 3 days of age. As with the septicemic form, usually more than one pig or the entire litter is affected. The first sign usually noticed is the fecal puddles on the floor. Affected piglets may still nurse in the early stages, but they gradually lose their appetite as the disease progresses. The feces vary from a pasty to watery consistency and are usually yellow to brown in color. When the diarrhea is profuse and watery, there will be no obvious staining of the perineum and hindquarters with feces, but the tails of the piglets will be straight and wet. Sick piglets occasionally vomit, although vomiting is not as prominent as with transmissible gastroenteritis. The temperature is usually normal or subnormal. The disease is progressive; diarrhea and dehydration continue, and the piglets become very weak and lie in lateral recumbency and make weak paddling movements. Within several hours they appear very dehydrated and shrunken, and they commonly die within 24 hours after the onset of signs if not treated. In severe outbreaks the entire litter may be affected and die within a few hours of birth. The prognosis is favorable if treatment is started early, before significant dehydration and acidosis occur.

Postweaning Diarrhea

The postweaning diarrhea (PWD) form of colibacillosis in piglets presents an economically important cause of death of weaned piglets. It is commonly seen within days of

weaning. In peracute cases piglets are found dead with an obviously dehydrated appearance, deeply sunken eyes, and cyanotic extremities. In less acute cases the first sign may be a loss in condition that is largely a result of dehydration. Diarrhea may not be apparent in all cases because fluid may just accumulate in the gut in some animals. If present, diarrhea can be watery to pasty, may contain blood in some instances, and may last between 1 and 5 days (see also "Post-weaning Diarrhea of Pigs").

CLINICAL PATHOLOGY

Culture and Detection of Organism

If septicemia is suspected, blood should be submitted for isolation of the organism and determination of its drug sensitivity. Blood for culture must be taken aseptically and inoculated directly into brain–heart infusion broth. Because of the limited sensitivity to detect bacteremia by a single culture, the blood sample should be repeated a few hours later to enhance recovery rate and confirm septicemia.

The **definitive etiologic diagnosis of enteric colibacillosis** depends on the isolation and characterization of *E. coli* from the intestines and the feces of affected animals. The best opportunity of making a diagnosis is when untreated representative affected animals are submitted for pathologic and microbiological examination. The distribution of the organism in the intestine; determination of the presence of F4 (K88), F5(K99), or F6 (987P) antigens; and the histopathologic appearance of the mucosa contribute to the diagnosis.

The routine culture of feces and intestinal contents for *E. coli* without determining their virulence determinants is of limited value. The laboratory tests used to identify enterotoxigenic F4 (K99) *E. coli* include a direct fluorescent antibody technique with conventional culturing methods and the ELISA, with or without monoclonal antibody, to detect the organism or the enterotoxin in the feces. DNA gene probes specific for genes encoding enterotoxin and adhesins are available and are being used to evaluate *E. coli* isolated from diarrheic animals. Isolates of the organism can also be examined for the presence of toxins using an enzyme immune assay test and latex agglutination test.

Detection of STEC in feces has relied on cytotoxicity testing and DNA hybridization. Several ELISAs are available, and monoclonal antibodies to the Shiga toxins ST1 and ST2 have been used to examine feces from animals. The isolation of *E. coli* O157:H7 has relied on its ability to ferment sorbitol. A sandwich ELISA using monoclonal antibodies to *E. coli* Shiga toxins 1 and 2 for capture and detection is available for detection of STEC in animal feces. A PCR test is also available for detection of ST genes in *E. coli* isolated from cattle, sheep, and pigs affected with diarrhea.

The determination of drug sensitivity of the *E. coli* isolated from the feces of diarrheic calves and piglets is commonly done, but it is of limited value without determining which isolate is enteropathogenic.

Hematology and Serum Biochemistry

A total and differential leukocyte count and remarkable changes in the fibrinogen concentration may indicate the presence of septicemia or severe intestinal infection. However, severely affected calves may not have grossly abnormal hemograms.[21] In enteric disease, the major changes in plasma composition are dehydration, electrolyte imbalance, and metabolic acidosis/acidemia. The total plasma osmolality tends to be decreased.

The packed cell volume and the total protein concentration of the blood will indicate the degree of dehydration, although the increase of total protein in calves with FTPI may underestimate the degree of dehydration. The blood urea nitrogen (BUN) concentration may be increased in severe cases because of inadequate renal perfusion. The blood bicarbonate concentration is markedly reduced, indicating the presence of metabolic acidosis. Decreased blood pH values represent acidemia. Calves with a venous blood pH below 7.0 require immediate parenteral therapy for acidemia. Other serum electrolytes are variable, but there may be a slight decrease in serum sodium and a slight increase in serum chloride. In severely dehydrated animals hyperkalemia may occur, which may result in bradyarrhythmia.[18]

Hematologic abnormalities associated with **septicemia** vary with the stage and severity of the disease. Abnormal neutrophil counts (neutrophilia or neutropenia), a left shift of neutrophils, and signs of toxicity in neutrophils are commonly seen in septic animals.[11,20,21] Hypoglycemia is another common, although certainly not pathognomonic, finding in septic calves.

NECROPSY FINDINGS

In **coliform septicemia** there may be no gross lesions, and the diagnosis may depend on the isolation of the organism from the filtering organs. In less severe cases there may be subserosal and submucosal hemorrhages. A degree of enteritis and gastritis may be present. Occasionally, fibrinous exudates are found in the joints and serous cavities, and there may be omphalophlebitis, pneumonia, and meningitis. The histologic features of such presentations of colibacillosis are those of septicemia and toxemia.

In **enteric colibacillosis** of piglets and calves the carcass appears dehydrated, but the intestine is flaccid and filled with fluid. In calves, the abomasum is usually distended with fluid and may contain a milk clot. Clots are typically absent in calves fed whey milk replacers that do not contain casein. The abomasal mucosa may contain numerous small hemorrhages. In both calves and pigs, the intestinal mucosae may appear normal or hyperemic, and there may be edema of the mesenteric lymph nodes. Mild atrophy or even fusion of jejunal and ileal villi is often seen, but the key microscopic observation is the **presence of bacilli adherent to the brush borders of enterocytes**. Ultrastructurally, there is increased epithelial cell loss from the villus about 12 hours after experimental inoculation of calves with an ETEC.

In calves affected with attaching and effacing *E. coli* there is pseudomembranous ileitis, mucohemorrhagic colitis, and proctitis. Microscopic examination of well-preserved gut segments reveals bacterial adherence, atrophy of ileal villi, and erosion of enterocytes.

In addition to traditional bacteriologic culture techniques, the ETEC may be identified by several tests, including indirect fluorescent antibody (IFA) tests specific for F4 (K88), F5 (K99), and F6 (987P) pilus antigens. The IFA tests can be performed on impression smears or frozen sections of ileal tissue, and the results are available within a few hours. Newer techniques such as DNA gene probes, enzyme immune assays, and latex agglutination tests are now available to identify those isolates that are enterotoxin producers and have adhesin properties.

During severe disease outbreaks it is often necessary to conduct the necropsy examination on diarrheic animals that have been killed specifically for the purpose of obtaining a definitive etiologic diagnosis. The combined use of bacteriologic, parasitologic, and virological methods, together with histologic and immunofluorescent studies of fresh intestinal tissue, will provide the most useful information about the location of the lesions and the presence of enteropathogens. Postmortem autolysis of the intestinal mucosae and invasion of the tissues by intestinal microflora occurs within minutes after death, so gut samples should be collected immediately following euthanasia of the animal.

Samples for Confirmation of Diagnosis

Coliform Septicemia

- Bacteriology—chilled spleen, lung, liver, culture swabs of exudates, umbilicus, meninges (culture)
- Histology—fixed samples spleen, lung, liver, kidney, brain, and any gross lesions

Enteric Colibacillosis

- Bacteriology—chilled segments of ileum and colon (including content; culture and/or FAT, latex agglutination, PCR)
- Histology—fixed duodenum, jejunum, ileum, colon, and mesenteric lymph node

Table 19-13 Possible causes of bacteremia/septicemia and acute neonatal diarrhea in farm animals

Calves	Piglets	Lambs and kids	Foals
Bacteremia/septicemia			
Escherichia coli	*E. coli*	*E. coli*	*E. coli*
Salmonella spp.	*Streptococcus*	*Salmonella* spp.	*Actinobacillus equuli*
Listeria monocytogenes	*L. monocytogenes*	*L. monocytogenes*	*Salmonella abortivoequina*
Pasteurella spp.		*Erysipelothrix rhusiopathiae*	*Salmonella typhimurium*
Streptococcus spp.			*Streptococcus pyogenes*
Pneumococcus spp.			*L. monocytogenes*
Acute neonatal diarrhea			
Enteropathogenic and enterotoxigenic *E. coli*	Enteropathogenic *E. coli*	*Clostridium perfringens* type C	Foal-heat diarrhea
Rotavirus	*Salmonella* spp.	*C. perfringens* type B	Rotavirus
Coronavirus	Transmissible	(lamb dysentery)	*C. perfringens* type B
Bovine torovirus (Breda virus)	gastroenteritis virus	Rotavirus	
Bovine calicivirus	*C. perfringens* type C	Caprine herpesvirus	
Bovine norovirus	(rarely A)		
Cryptosporidium spp.	*Clostridium difficile*		
Giardia spp.	Rotavirus		
Salmonella spp.	PRRSV		
Eimeria spp. (calves at least 3 weeks old)	*Isospora* spp.		
C. perfringens type C			

PRRSV, porcine reproductive and respiratory syndrome virus.

DIFFERENTIAL DIAGNOSIS

The definitive etiologic diagnosis of septicemic colibacillosis is dependent on the laboratory isolation of the causative agent, which is usually a single species or organism. The septicemias of the newborn cannot be distinguished from one another clinically. The definitive etiologic diagnosis of enteric colibacillosis in newborn calves and piglets may be difficult and often inconclusive because the significance of other organisms in the intestinal tract and feces of diarrheic animals cannot be easily determined.

Table 19-13 lists the possible causative agents of diarrhea and septicemia in newborn farm animals. Using the combined diagnostic approach of detection of enteropathogens in the feces before death and in the intestinal mucosa after death, it is possible to identify where ETEC, rotavirus, coronavirus, *Salmonella* spp., and *Cryptosporidium* spp. appear to be the only or principal causative agents. However, mixed infections are more common than single infections.

Every effort that is economically possible should be made to obtain an etiologic diagnosis. This is especially important when outbreaks of diarrhea occur in a herd or when the disease appears to be endemic. The use of an interdisciplinary approach will increase the success of diagnosis. This includes making a visit to the farm or herd and making a detailed epidemiologic investigation of the problem. The diagnosis depends heavily on the epidemiologic findings, the microbiological and pathologic findings, and sometimes on the results of treatment.

The major difficulty is to determine whether or not the diarrhea is infectious in origin and to differentiate it from dietetic diarrhea, which is most common in hand-fed calves and in all newborn species that are sucking high-producing dams. In dietetic diarrhea the feces are voluminous and pasty to gelatinous in consistency; the animal is bright and alert and is usually still sucking, but some may be inappetent.

TREATMENT

Coliform Septicemia

Intensive critical care is required for the treatment of neonatal coliform septicemia. Early identification of animals suspected of being septicemic and early therapeutic intervention are important determinants of the treatment success. Evidence from human medicine indicates that the survival rate must be expected to decrease by 10% for every hour antimicrobial therapy is delayed in patients in septic shock.[22] A recent consensus statement in human medicine recommends initiation of intravenous antimicrobial therapy within the first hour after having recognized severe septicemia.[23] Thus, in most cases antimicrobial therapy has to be initiated before confirmatory culture results are available.

Although *E. coli* may be cultured from the blood of septicemic foals and calves, a significant percentage of isolates are gram-positive, which justifies the use of antimicrobials that have a broad spectrum. Antimicrobials are given parenterally and may be given continuously intravenously, more than once daily and daily until recovery is apparent. Isolation of the organisms from blood and determination of drug sensitivity constitute the ideal protocol. Intravenous fluid and electrolyte therapy are administered continuously until recovery is apparent (see "Principles of Fluid and Electrolyte Therapy"). Whole blood transfusions are used in calves and foals, especially when immunoglobulin deficiency is suspected from the history or is determined by measurement of serum immunoglobulins of blood. In one series on neonatal septicemia in calves, in which *E. coli* accounted for 50% of the bacterial isolates, the survival rate was only 12%.

Enteric Colibacillosis

The considerations for treatment of enteric colibacillosis include the following:

- Fluid and electrolyte replacement
- Antimicrobial and immunoglobulin therapy
- Antiinflammatory therapy
- Antimotility drugs
- Intestinal protectants
- Alteration of the diet
- Probiotics
- Clinical management of outbreaks

Fluid and Electrolyte Replacement

The dehydration, acidosis, and electrolyte imbalance are corrected by the parenteral and oral use of simple or balanced electrolyte solutions. The provision of fluid therapy in diarrheic dehydrated calves under field conditions in veterinary practice has been described. It is important to obtain an adequate history of the case, including age of the calf, duration of the diarrhea, and all treatments already given by the owner. The physical examination of the calf includes a standard clinical examination with emphasis on evaluating the degree of dehydration and acidosis.

Dehydration is evaluated by two clinical observations:

- **Skin elasticity**. The skin of the middle of the neck is better than the eyelid. A portion of the skin is tented and twisted for 1 second, and then the time to return to the initial position is measured—less than 2 seconds in the normal calf, 6 seconds in moderate (8%) dehydration, and more than 8 seconds in severe (12%) dehydration (Table 19-12).
- **Position of eyeball in the orbit and extent of enophthalmos**. This is determined by measuring the distance between the globe and the orbit. The eyeball is not sunken in healthy calves. Degrees of dehydration of 4%, 8%, and 12% are represented by 2-mm, 4-mm, and 7-mm enophthalmos, respectively (Table 19-12).

The degree of metabolic acidosis can be evaluated by determining the degree of obtundation, muscular tone, ability to stand, intensity of the sucking reflex, temperature of the inside of the oral cavity, and age of the calf that correlate with an estimate of the **base deficit**. The following categories for diarrheic calves are being used under field conditions:

1. Calves with good muscular tone and the ability to stand, strong suck reflex, and warm oral cavity have no base deficit if younger than 8 days of age and up to 5 mEq/L if older than 5 days.
2. Calves that can stand, have a slightly cool oral cavity, and have a weak suck reflex have a base deficit of 5 mEq/L if under 8 days of age and 10 mEq/L if older than 8 days.
3. Calves in sternal recumbency with a cool oral cavity and no suck reflex have a base deficit of 10 mEq/L if under 8 days of age and 15 mEq/L if older than 8 days.
4. Calves in lateral recumbency that lack a suck reflex and have a cold oral cavity have a base deficit of 10 mEq/L if under 8 days of age and 20 mEq/L if older than 8 days.

Categorizing Diarrheic Calves Into Treatment Groups

Based on the history and clinical findings, affected calves can be divided into the following categories according to the type of therapy required and which is most economical:

1. **Oral fluid therapy**—calves with a history of acute diarrhea, less than 7% dehydrated, slightly dry oral mucosa, good suck reflex, good muscle tone, alert, able to stand, and warm mouth. These can be treated with oral fluids and electrolytes.
2. **Oral fluid therapy and hypertonic saline solution**—calves with 7% to 9% dehydration and slight acidosis, weak suck reflex, good muscular tone, and warm mouth. Administer hypertonic saline solution (7.5% NaCl) intravenously at 3 to 4 mL/kg BW in 5 minutes. Assure voluntary intake of oral fluids, or administer oral fluids and electrolytes by stomach tube at 40 to 60 mL/kg BW. Reevaluate in 6 to 8 hours.
3. **Intravenous fluid therapy with alkalinizing agents**—calves that are more than 9% dehydrated, have dry and cool oral mucous membranes, are recumbent, have no suck reflex, and are very depressed. Provide intravenous replacement and maintenance fluid and electrolyte therapy including an alkalinizing agent for a period of 6 to 8 hours and up to 24 to 36 hours if necessary.

The details for parenteral and oral fluid and electrolyte therapy are described under "Principles of Fluid and Electrolyte Therapy."

Antimicrobial Therapy

Antimicrobials have been used extensively for the specific treatment of colibacillosis in calves and piglets because it was assumed that an infectious enteritis was present. It has been difficult to evaluate the efficacy of antimicrobials for the treatment of enteric colibacillosis because of the complex nature of the interactive factors that affect the outcome in naturally occurring cases. These include the presence of mixed infections, the effects of whether or not milk is withheld from the diarrheic calves, the effects of the immune status of individual calves, the variable times after the onset of diarrhea when the drugs are given, the possible presence of antimicrobial resistance, and the confounding effects of supportive treatment such as electrolyte and fluid therapy.

Change in Small Intestinal Bacterial Flora in Calves With Diarrhea

There has been a paradigm shift in the last 40 years toward categorizing an episode of calf diarrhea as being the result of a specific etiologic agent, such as rotavirus, coronavirus, cryptosporidia, *Salmonella* spp., or ETEC. Although the etiologic approach has correctly focused attention on preventive programs, including vaccination and optimizing transfer of colostral immunity, the approach has diverted attention from the universal finding of all studies, which is that calves with diarrhea of whatever etiology have coliform bacterial overgrowth of the small intestine.

Studies completed more than 70 years ago documented increased numbers of *E. coli* bacteria in the abomasum, duodenum, and jejunum of scouring calves. Moreover, calves severely affected with diarrhea had increased numbers of *E. coli* bacteria in the anterior portion of their intestinal tracts compared with mildly affected animals. More recent studies have consistently documented the fact that calves with naturally acquired diarrhea, regardless of age and the etiologic cause for the diarrhea, have altered small intestinal bacterial flora. Specifically, *E. coli* bacterial numbers were increased 5- to 10,000-fold in the duodenum, jejunum, and ileum of calves with naturally acquired diarrhea, even when the diarrhea was not attributable to ETEC, and where rotavirus and coronavirus were identified in the feces. The largest increase in *E. coli* bacterial numbers occurs in the distal jejunum and ileum, whereas the *E. coli* or coliform bacterial numbers in the colon and feces are similar or higher for calves with diarrhea than calves without diarrhea, with *E. coli* being more numerous in the feces of colostrum-deprived than colostrum-fed calves. Small intestinal overgrowth with coliform bacteria can persist after departure of the initiating enteric pathogen.

In calves with naturally acquired diarrhea, increased small-intestinal colonization with *E. coli* has been associated with impaired glucose, xylose, and fat absorption.

Mixed infections with enteric pathogens are commonly diagnosed in calves with naturally acquired diarrhea, and the clinical signs and pathologic damage associated with rotavirus infection are more severe when *E. coli* is present than when it is absent. Primary viral morphologic damage to the small intestine also facilitates systemic invasion by normal intestinal flora, including *E. coli*.

In calves with experimentally induced ETEC diarrhea, colonization of the small intestine by *E. coli* has been associated with impaired glucose and lactose absorption, decreased serum glucose concentration, and possibly increased susceptibility to cryptosporidial infection.

In summary, calves with diarrhea have increased coliform bacterial numbers in the small intestine, regardless of etiology, and this colonization is associated with altered small-intestinal function, morphologic damage, and increased susceptibility to bacteremia. It therefore follows that administration of antimicrobials that decrease small-intestinal coliform bacterial numbers in calves with diarrhea may prevent the development of bacteremia, decrease mortality, and decrease morphologic damage to the small intestine, thereby facilitating digestion and absorption and increasing growth rate.

Incidence of Bacteremia in Calves With Diarrhea

Calves with diarrhea are more likely to have FTPI, and this group of calves, in turn, is more likely to be bacteremic. Colostrum-deprived calves that subsequently developed diarrhea were frequently bacteremic, whereas bacteremia occurred much less frequently in colostrum-fed calves that developed diarrhea.

Based on field studies of diarrheic calves, it can be assumed that, **on average, 30% of**

severely ill calves with diarrhea are bacteremic, with *E. coli* being the predominantly isolated pathogen. The risk of bacteremia is higher in calves with FTPI than in calves with adequate transfer of passive immunity, and the risk of bacteremia is higher in calves 5 days of age or younger. Veterinarians should also assume that 8% to 18% of diarrheic calves with adequate transfer of passive immunity and systemic illness are bacteremic. The prevalence of bacteremia is sufficiently high in systemically ill calves that effective antimicrobial treatment for potential bacteremia should be routinely instituted, with emphasis on treating potential *E. coli* bacteremia, regardless of transfer of passive immunity status and treatment cost. Withholding an effective treatment for a life-threatening condition, such as bacteremia in calves with diarrhea, cannot be condoned on animal welfare grounds.

Antimicrobial Susceptibility of Fecal *Escherichia coli* Isolates

The most important determinant of antimicrobial efficacy in calf diarrhea is obtaining an effective antimicrobial concentration against bacteria at the sites of infection (small intestine and blood). The results of fecal antimicrobial susceptibility testing have traditionally been used to guide treatment decisions; however, susceptibility testing in calf diarrhea probably has clinical relevance only when applied to fecal isolates of ETEC or pathogenic *Salmonella* spp. and blood culture isolates from calves with bacteremia. Validation of susceptibility testing as being predictive of treatment outcome for calves with diarrhea is currently lacking.

The ability of fecal bacterial culture and antimicrobial susceptibility testing using the Kirby–Bauer technique to guide treatment in calf diarrhea is questionable when applied to fecal *E. coli* isolates that have not been identified as enterotoxigenic. There do not appear to be any data demonstrating that fecal bacterial flora is representative of the bacterial flora of the small intestine, which is the physiologically important site of infection in calf diarrhea. Marked changes in small-intestinal bacterial populations can occur without changes in fecal bacterial populations, and the predominant strain of *E. coli* in the feces of a diarrheic calf can change several times during the diarrhea episode. Furthermore, and most importantly, 45% of calves with diarrhea had different strains of *E. coli* isolated from the upper and lower small intestine, indicating that fecal *E. coli* strains are not always representative of small-intestinal *E. coli* strains. Marked discrepancies in antimicrobial resistance among *E. coli* strains isolated from different segments of the upper and lower intestinal tract of healthy veal calves at slaughter have also been reported in a more recent study.[24]

An additional bias present in most antimicrobial susceptibility studies conducted on fecal *E. coli* isolates is that data are frequently obtained from dead calves, which are likely to be treatment failures. The time since death is also likely to be an important determinant of the value of fecal culture because such a rapid proliferation of bacteria occurs in the alimentary tract after death that the results of examinations made on dead calves received at the laboratory can have little significance. Calves that die of diarrhea are likely to have received multiple antimicrobial treatments, and preferential growth of antimicrobial-resistant *E. coli* strains starts within 3 hours of antimicrobial administration. A further concern with fecal susceptibility testing is that the Kirby–Bauer breakpoints (minimum inhibitory concentration [MIC]) are not based on typical antimicrobial concentrations in the small intestine and blood of calves. Studies documenting the antimicrobial susceptibility of *E. coli* isolates from the small intestine of untreated calves, based on achievable drug concentrations and dosage regimens, are urgently needed. Until these data are available, it appears that antimicrobial efficacy is best evaluated by the clinical response to treatment, rather than the results of in vitro antimicrobial susceptibility testing performed on fecal *E. coli* isolates. Thus, the value of antimicrobial susceptibility testing as a tool to guide the choice of an antibiotic to treat enterotoxigenic colibacillosis must currently be considered as very limited. Nonetheless, antimicrobial susceptibility testing presents an important tool to monitor the development of resistances not only of pathogens, but also of so-called indicator bacteria normally isolated in healthy animals in the field.[25,26] Because antimicrobial resistance can be transferred via plasmids from apathogenic bacteria to pathogens, monitoring trends in resistance patterns in the field is of critical importance.

Surveillance for Antimicrobial Resistance in *Escherichia coli* Isolates

The purpose of monitoring antimicrobial resistance through so-called indicator bacteria is to avoid misjudgment (overestimation) of resistance levels that would be extrapolated from resistance of pathogenic bacteria.[24] As mentioned earlier, pathogens isolated from sick or deceased animals have frequently been exposed to antimicrobial therapy, which is likely to alter resistance patterns. A comparison of antibiotic resistance for *E. coli* populations isolated from groups of diarrheic and control calves in the United Kingdom found a higher incidence of antibiotic-resistant *E. coli* in samples obtained from farms with calf diarrhea than from farms without the disease. Considering all samples, bacterial colonies in 84% were resistant to ampicillin, in 13% to Apramycin, and in 6% to nalidixic acid. Antibiotic resistance among ETEC from piglets and calves with diarrhea in a diagnostic laboratory survey of one geographic area in Canada over a 13-year period found that the least resistance occurred against ceftiofur for all isolates, followed by apramycin and gentamicin for porcine and florfenicol for bovine isolates.

In a UK study over a 5-year period, *E. coli* isolates from calves with diarrhea became more resistant to furazolidone, trimethoprim-potentiated sulfonamide, clavulanic-acid-potentiated amoxicillin, and tetracycline. *E. coli* strains from outbreaks of diarrhea in lambs in Spain became increasingly resistant to nalidixic acid, enoxacin, and enrofloxacin. Some antimicrobial-resistant *E. coli* strains from diarrheic calves in the United States may possess a chromosomal *flo* gene that specifies cross-resistance to both florfenicol and chloramphenicol, and its presence among *E. coli* isolates of diverse genetic backgrounds indicates a distribution much wider than previously thought. In Spain, 5.9% of *E. coli* strains from cattle were resistant to nalidixic acid, and 4.9% were resistant to enrofloxacin and ciprofloxacin. In sheep and goats, only 0.5% and 1.4%, respectively, of the strains were resistant to nalidixic acid, and none was resistant to fluoroquinolones. Most of the quinolone-resistant strains were nonpathogenic strains isolated from cattle. Susceptibility data obtained from 10 European countries for the years 2002 to 2004 revealed that although there was a generally high prevalence of resistance of *E. coli* isolated from diarrheic calves, resistance patterns varied considerably between countries.[25] Generally high resistance of *E. coli* in the range of 50% or higher was reported from most countries for ampicillin, streptomycin, sulfonamides, trimethoprim, combinations of trimethoprim and sulfonamides, and tetracyclines.[25] Although resistance of *E. coli* isolated from diarrheic calves against fluoroquinolones was rare in several countries, resistance rates at or above 20% were reported from Spain, Belgium, and France.[25] In certain regions of Italy the incidence of enrofloxacin-resistant *E coli* strains was reported to have increased from 14.2% in 2002 to over 40% in 2008.[27]

The CTX-M-14-like enzyme has been detected in *E. coli* recovered from the feces of diarrheic dairy calves in Wales. The enzyme is an extended-spectrum beta-lactamase (ESBL), which confers resistance to a wide range of beta-lactam (penicillin and cephalosporin) compounds. Organisms possessing ESBLs are considered to be resistant to second-, third-, and fourth-generation cephalosporins, and in vitro resistance to amoxicillin/clavulanate among producers is variable, reflecting the amount of beta-lactamase produced. In addition to this enzyme, the isolates produced a TEM-35 (IRT-4) beta-lactamase that conferred resistance to the amoxicillin/clavulanate combination. These two enzymes confer resistance to all the beta-lactamase compounds approved for veterinary use in the United

Kingdom. Thus their occurrence in animals may be an important development for both animal and public health. ESBLs in human infections have emerged as a significant and developing problem, occurring in patients in the community and in those with recent hospital contact. Spread of this form of resistance in bacteria affecting the animal population could have serious implications for animal health, rendering many therapeutic options redundant.

Antimicrobial resistance to intestinal bacteria also occurs in dairy calves fed milk from cows treated with antibiotics and has been associated with the prophylactic administration of medicated milk replacer.[28] The resistance increases with higher concentrations of antibiotics in the milk. Susceptibility of fecal and environmental *E. coli*, *Salmonella* spp., and *Campylobacter* spp. to tetracyclines was monitored on farms during use of medicated milk replacer and after discontinuation of this practice. Discontinuing the use of medicated milk replacer resulted in increased susceptibility of these organisms to tetracyclines within 3 months, without causing an increase of disease occurrence.[28]

Antimicrobial Susceptibility of Blood *Escherichia coli* Isolates

The Kirby–Bauer technique for antimicrobial susceptibility testing has more clinical relevance for predicting the clinical response to antimicrobial treatment when applied to blood isolates rather than fecal isolates. This is because the Kirby–Bauer breakpoints (MICs) are based on achievable antimicrobial concentrations in human plasma and MIC_{90} values for human *E. coli* isolates, which provide a reasonable approximation to achievable MIC values in calf plasma and MIC_{90} values for bovine *E. coli* isolates. Unfortunately, susceptibility results are not available for at least 48 hours, and very few studies have documented the antimicrobial susceptibility of blood isolates in calves with diarrhea. In a 1997 study of dairy calves in California, the antimicrobial susceptibility of isolates from the blood of calves with severe diarrhea or illness produced the following results: ceftiofur, 19/25 (76%) sensitive; potentiated sulfonamides, 14/25 (56%) sensitive; gentamicin, 12/25 (48%) sensitive; ampicillin, 11/25 (44%) sensitive; tetracycline, 3/25 (12%) sensitive, although there was a clinically significant year-to-year difference in the results of susceptibility testing that may have reflected different antimicrobial administration protocols on the farm.

Evidence-Based Recommendations for Antimicrobial Treatment of Diarrheic Calves

The four critical measures of success of antimicrobial therapy in calf diarrhea are as follows (in decreasing order of importance): (1) mortality rate, (2) growth rate in survivors, (3) severity of diarrhea in survivors, and (4) duration of diarrhea in survivors.

In his review of the literature on the use of antibiotics for the treatment of calf diarrhea, Constable concluded that the statement that oral or parenteral antimicrobials should not be used is not supported by a critical evidence-based review of the literature.[29] The arguments used to support a nonantimicrobial treatment approach have included the following:

- Orally administered antimicrobials alter intestinal flora and function and thereby induce diarrhea, which has been documented on more than one occasion with chloramphenicol, neomycin, and penicillin.
- Antimicrobials harm the "good" bacteria in the small intestine more than the "bad" bacteria (an undocumented claim in the calf).
- Antimicrobials are not effective (a statement that is clearly not supported by the results of some published peer-reviewed studies).
- Antimicrobial administration promotes the selection of antimicrobial resistance in enteric bacteria.

In calves with diarrhea and moderate to severe systemic illness, the positive predictive value (0.65) of clinical tests (sensitivity = 0.39, specificity = 0.91) and the positive predictive value (0.77) of laboratory tests (sensitivity = 0.40, specificity = 0.95) for detecting bacteremia are too low, assuming reasonable estimates for the prevalence of bacteremia (30%). Accordingly, it is recommended that clinicians routinely assume that 30% of ill calves with diarrhea are bacteremic and that bacteremia constitutes a threat to the life of the calf. Antimicrobial treatment of diarrheic calves should therefore be practiced and focused against *E. coli* in the small intestine and blood because these constitute the two sites of infection. In addition, the antimicrobial must reach therapeutic concentrations at the site of infection for a long enough period (the treatment interval) and, ideally, have only a narrow gram-negative spectrum of activity to minimize collateral damage to other enteric bacteria. Fecal bacterial culture and antimicrobial susceptibility testing is not recommended in calves with diarrhea because fecal bacterial populations do not accurately reflect small-intestinal or blood bacterial populations, and the breakpoints for susceptibility test results have not been validated. Antimicrobial efficacy is therefore best evaluated by the clinical response to treatment.

The efficacy of antimicrobial therapy can vary with the route of administration and when given orally, whether the antimicrobial is dissolved in milk, oral electrolyte solutions, or water. Oral antimicrobials administered as a bolus or contained in a gelatin capsule are deposited into the rumen and therefore have a different serum concentration–time profile than antimicrobials dissolved in milk replacer that are suckled by the calf. Antimicrobials that bypass the rumen are not thought to alter rumen microflora, potentially permitting bacterial recolonization of the small intestine from the rumen. Finally, when oral antimicrobials are administered to calves with diarrhea, the antimicrobial concentration in the lumen of the small intestine is lower and the rate of antimicrobial elimination faster than in healthy calves.

In the United States parenterally administered oxytetracycline and sulfachloropyridiazine and orally administered amoxicillin, chlortetracycline, neomycin, oxytetracycline, streptomycin, sulfachloropyridazine, and sulfamethazine are currently labeled for the treatment of calf diarrhea. Unfortunately, there is little published data supporting their efficacy in treating calves with diarrhea. Extralabel antimicrobial use (excluding prohibited antimicrobials) is therefore justified in treating calf diarrhea because of the apparent lack of published studies documenting clinical efficacy of antimicrobials with a label claim and because the health of the animal is threatened; suffering or death may result from failure to treat systemically ill calves.

Administration of Oral Antimicrobials to Treat *Escherichia coli* Overgrowth of the Small Intestine

Based on published evidence for the oral administration of these antimicrobial agents, only amoxicillin can be recommended for the treatment of diarrhea; dosage recommendations are amoxicillin trihydrate (10 mg/kg every 12 h) or amoxicillin trihydrate–clavulanate potassium (10 mg/kg amoxicillin trihydrate and 2.5 mg/kg clavulanate potassium every 12 h) for at least 3 days; the latter constitutes extralabel drug use. Concurrent feeding of milk and amoxicillin does not change the bioavailability of amoxicillin, although amoxicillin is absorbed faster when dissolved in an oral electrolyte solution than in milk replacer, and absorption is slowed during endotoxemia, presumably because of a decrease in abomasal emptying rate. Amoxicillin trihydrate is preferred to ampicillin trihydrate for oral administration in calves because it is labeled for the treatment of calf diarrhea in the United States and is absorbed to a much greater extent. However, a field study comparing oral amoxicillin (400 mg every 12 h) and ampicillin (400 mg every 12 h) treatments for diarrhea reported similar proportions of calves with a good to excellent clinical response (79%, 49/62 for amoxicillin bolus; 80%, 59/74 for amoxicillin powder; 65%, 47/65 for ampicillin bolus; $p > 0.30$ for all comparisons). The addition of clavulanate potassium to amoxicillin trihydrate is recommended because clavulanate potassium, although not having a direct antimicrobial

effect, is a potent irreversible inhibitor of beta-lactamase, increasing the antimicrobial spectrum of activity.

Oral administration of potentiated sulfonamides is not recommended for treating calf diarrhea because of the lack of efficacy studies. Gentamicin (50 mg/calf orally every 12 h) markedly decreased *E. coli* bacterial concentrations in the feces of healthy calves, and treatment with gentamicin has been shown to improve stool consistency in calves with experimentally induced *E. coli* diarrhea. However, oral administration of gentamicin is not recommended because antimicrobials administered to calves with diarrhea should have both local and systemic effects, and orally administered gentamicin is poorly absorbed.

Colistin administered orally is frequently used in calves in piglets to treat enterotoxic colibacillosis. Oral colistin will decrease the number of *E. coli* bacteria in the intestinal lumen and thereby the amount of enterotoxin affecting the intestinal mucosa and can present an effective treatment of uncomplicated cases of enteric colibacillosis. Because colistin is poorly absorbed from the alimentary tract, this treatment is not indicated in cases of suspected septicemia.

Oxytetracycline and chlortetracycline are not recommended for the oral treatment of bacteremia, although tetracyclines may have some efficacy for treating *E. coli* bacterial overgrowth of the small intestine. Tetracyclines are bound to calcium, and oral bioavailability when administered with milk is 46% for oxytetracycline and 24% for chlortetracycline.

Florfenicol achieves high concentrations in the lumen of the small intestine and is 89% absorbed when orally administered to milk-fed calves; however, florfenicol does not provide the most appropriate antimicrobial for treating calf diarrhea, because the MIC_{90} for *E. coli* is very high at 25 µg/mL and florfenicol (11 mg/kg orally) was shown to fail to reach the MIC_{90} value in plasma.

Fluoroquinolones clearly have proven efficacy in treating calf diarrhea, and a label indication exists in Europe for oral and parenteral enrofloxacin and oral marbofloxacin for the treatment of calf diarrhea. Oral fluoroquinolones have a high oral bioavailability. However, it must be emphasized that extralabel use of the fluoroquinolone class of antimicrobials in food-producing animals in the United States is illegal and obviously not recommended. Also, in other countries it may be illegal to use some of the antimicrobials mentioned here because of the regulations regarding their use in food-producing animals.

The indiscriminate use of antibiotics in milk replacers for the treatment of newborn calves and piglets is widespread and must be viewed with concern when the problem of drug-resistance transfer from animal to animal and to humans is considered.

In calves with diarrhea and no systemic illness (normal appetite for milk or milk replacer, no fever), it is recommended that the clinician should monitor the health of the calf and should not administer oral antimicrobials.

Administration of Parenteral Antimicrobials to Treat *Escherichia coli* Bacteremia

A common and widely recommended treatment is ceftiofur (2.2 mg/kg intramuscularly/subcutaneously every 12 h) for at least 3 days. Ceftiofur is a broad-spectrum third-generation cephalosporin and beta-lactam antimicrobial that is resistant to the action of beta-lactamase; the MIC_{90} for *E. coli* is less than 0.25 µg/mL, the recommended dosage schedule maintains free plasma antimicrobial concentrations at the desired value of four times the MIC_{90} value for the duration of treatment in 7-day-old calves, and 30% of the active metabolite of ceftiofur (desfuroylceftiofur) is excreted into the intestinal tract of cattle, providing antimicrobial activity in both the blood and the small intestine. Parenteral (2 mg/kg, intramuscularly once) administration of ceftiofur hydrochloride decreased mortality rate and the severity of diarrhea in pigs with experimentally induced enteric colibacillosis, although these pigs were not suspected to be bacteremic. The beneficial effects of parenteral ceftiofur in these pigs was attributed to decreasing intestinal luminal concentration of pathogenic *E. coli.* Administration of ceftiofur to treat bacteremia and diarrhea in calves constitutes extralabel drug use.

In those countries where the use of fluoroquinolones in food-producing animals is permitted for this indication, parenteral administration to calves with diarrhea has been recommended because of their broad-spectrum bactericidal activity, particularly against gram-negative bacteria. It must be emphasized that extralabel use of the fluoroquinolone class of antimicrobials in food-producing animals in the United States and other countries is illegal and obviously not recommended.

Cephalosporins and fluoroquinolones are among the most commonly used antimicrobials to treat colibacillosis in farm animals because of their proven efficacy and because they have largely maintained their activity against *E. coli.* Recent trends of decreasing susceptibility of *E. coli* and other pathogens mainly to fluoroquinolones and to a lesser degree to third- and fourth-generation cephalosporins have, however, been reported and present a serious public health issue (see following discussion under "Use of Antimicrobials That Are of Critical Importance for Human and Veterinary Medicine").[25-27]

Another recommended treatment is parenteral amoxicillin trihydrate or ampicillin trihydrate (10 mg/kg intramuscularly every 12 h) for at least 3 days. Although parenteral ampicillin has proven efficacy in treating naturally acquired diarrhea, whereas ceftiofur has unproven efficacy, the broad-spectrum beta-lactam antimicrobials amoxicillin and ampicillin are theoretically inferior to ceftiofur because parenterally administered ampicillin and amoxicillin reach lower plasma concentrations and require a higher MIC than ceftiofur, and they are not beta-lactamase-resistant. The intramuscular administration of amoxicillin and ampicillin is preferable over subcutaneous administration because the rate and extent of absorption are superior after intramuscular injection.

Parenteral treatment with potentiated sulfonamides (20 mg/kg sulfadiazine with 5 mg/kg trimethoprim, intravenously or intramuscularly depending on the formulation characteristics, every 24 h for 5 d) is also widely used. The efficacy of potentiated sulfonamides has only been proved when treatment commenced before clinical signs of diarrhea were present. It is therefore unknown whether potentiated sulfonamides are efficacious when administered to calves with diarrhea and depression, although it is likely that potentiated sulfonamides are efficacious in the treatment of salmonellosis.

Parenteral administration of gentamicin and other aminoglycosides (amikacin, kanamycin) cannot currently be recommended as part of the treatment for calf diarrhea because of the lack of published efficacy studies, prolonged slaughter withdrawal times (15 to 18 months), potential for nephrotoxicity in dehydrated animals, and availability of amoxicillin, ampicillin, and ceftiofur.

Chloramphenicol had proven efficacy in treating calf diarrhea resulting from *Salmonella enterica* serotypes Bredeney and Dublin, but it is now illegal for use in food-producing animals in the United States and in many other countries. The related antimicrobial florfenicol (20 mg/kg intramuscularly) failed to reach the MIC_{90} value in plasma and only exceeded the MIC_{90} value for less than 60 minutes when administered intravenously (11 to 20 mg/kg IV).

In calves with diarrhea and no systemic illness (normal appetite for milk or milk replacer, no fever), the clinician should monitor the health of the calf and refrain from administering oral or parenteral antimicrobials.

Use of Antimicrobials That Are of Critical Importance for Human and Veterinary Medicine

Antimicrobials commonly used for the treatment of colibacillosis in food-producing animals include third- and fourth-generation cephalosporins and fluoroquinolones, some of which have a label for the treatment of septicemia caused by *E.coli* in calves in some European and other countries and some of which can be used in an extralabel

manner in certain countries.[30] These classes of antimicrobials are considered to be **critically important for human and animal health,** and thus recent reports of increasing prevalence of resistance of *E. coli*, *Salmonella* spp., and *Enterobacter* spp. against these classes of antimicrobials are very concerning.[25-27] Although there appears to be general consensus that these antimicrobials should be used restrictively in veterinary medicine, there is currently no harmonized approach on prudent use of cephalosporins and fluoroquinolones in animals. Guidance on prudent use of antimicrobials for animals have been published in many countries, but most are on a general level, and cephalosporins and fluoroquinolones are not always specially addressed.[30]

The World Organization for Animal Health (OIE) issued the following recommendations for these classes of antimicrobials:[31]

- They are not to be used as preventive treatment applied by feed or water in the absence of clinical signs.
- They are not to be used as first-line treatment unless justified. When used in a second-line treatment, such use should ideally be based on the results of bacteriologic tests.
- Extralabel/off-label use should be limited and reserved for instances in which no alternatives are available. Such use should be in agreement with the national legislature in force.

Immunoglobulin Therapy

One of the important factors determining whether or not an animal will survive enteric colibacillosis is the serum immunoglobulin status of the animal before it develops the disease. The prognosis is unfavorable if the level of immunoglobulin is low at the onset of diarrhea, regardless of intensive fluid and antimicrobial therapy. Most of the literature on therapy omits this information and is therefore difficult to assess. There is ample evidence that the mortality rate will be high in diarrheic calves that are deficient in serum immunoglobulin, particularly IgG, in spite of exhaustive antimicrobial and fluid therapy. This has stimulated interest in the possible use of purified solutions of bovine gammaglobulin in diarrheic calves that are hypogammaglobulinemic. However, they must be given by the intravenous route and in large amounts, the cost of which would be prohibitive. In addition, they are unlikely to be of value once the calf is affected with diarrhea; they are protective and probably not curative. Whole blood transfusion to severely affected calves may be used as a source of gammaglobulin, but unless given in large quantities will not significantly elevate serum immunoglobulin concentrations in deficient calves. Limited controlled trials indicate that there is no significant difference in the survival rate of diarrheic calves treated with either a blood transfusion daily for 3 days; fluid therapy given orally, subcutaneously, or intravenously, depending on the severity of the dehydration; or fluid therapy with antibiotics. Those calves that survived, regardless of the type of therapy, had high immunoglobulin concentrations before they developed diarrhea. This emphasizes the importance of the calf ingesting liberal quantities of colostrum within the first few hours after birth.

Analgesic and Antiinflammatory Therapy

Pain in sick farm animals has become an important issue for veterinarians and producers and is perceived as important animal welfare issue by the public. Adequate pain management should be part of any state-of-the-art treatment approach.

Diarrhea can be accompanied by abdominal pain as a result of intestinal inflammation and cramping. In addition to controlling pain, the main objectives of antiinflammatory therapy in animals with colibacillosis are to control the inflammatory process in the intestinal tract and to ameliorate the effects of endotoxemia and septicemia.[32] Several field studies reported that diarrheic calves receiving nonsteroidal antiinflammatory drugs (NSAIDs) in conjunction with fluid therapy showed less signs of pain, made a faster recovery, and had better weight gains in the reconvalescent period.[33] Although the underlying mechanisms do not appear to have been studied in detail, the proven beneficial effects of several NSAIDs have been attributed to their analgesic, antiinflammatory, antipyretic, and antisecretory properties.

Two broad categories of antiinflammatory agents that are available are the corticosteroids and the NSAIDs. Little evidence documenting the efficacy of corticosteroids for the treatment of calf diarrhea is available, but the use of this class of antiinflammatory drugs has been discouraged on the theoretical grounds that diarrheic calves already tend to have higher concentrations of plasma cortisol of endogenous origin and because of the immunosuppressive effect of these compounds.[32]

The efficacy of different NSAIDs such as meloxicam, ketoprofen, or flunixin meglumine in diarrheic calves that were systemically ill has been investigated in several studies.[32] A single treatment with meloxicam (0.5 mg/kg intravenously [IV]) and treatment with ketoprofen (6 mg/kg IV) twice, 4 hours apart, were both found to improve general attitude, the fecal score, and the feed intake of systemically affected calves with diarrhea.[32] Flunixin meglumine (2.2 mg/kg IV) hastened clinical recovery, but only for animals that had visible amounts of blood in feces.[34]

Because treatment with NSAIDs in diarrheic animals bears the risk of causing renal damage by further decreasing renal perfusion in already dehydrated animals, adequate oral and/or parenteral fluid therapy must be assured. An empirical guideline posits that treatment with NSAIDs should be limited to a single treatment whenever possible but should not exceed three treatments, a recommendation that has been justified by the risk of abomasal ulceration that is associated with prolonged use of these antiinflammatory agents.[32]

Antimotility Drugs

Administration of substances reducing intestinal motility to treat diarrhea in farm animals is advocated by some veterinarians. Compounds such as hyoscine-N-butylbromide and atropine have a proven inhibitory effect on intestinal motility, which undisputedly results in a rapid decrease of the fecal output in diarrheic patients. Although reducing fecal production may be interpreted as positive treatment outcome, it can also be seen as sequestration of gut fluid in the intestinal tract. Delaying the excretion of intestinal contents in patients suffering from malabsorptive diarrhea bears the risk of enhanced fermentation of unabsorbed carbohydrates and other nutrients. This could not only exacerbate enteral dysbiosis, but also the accumulation of D-lactic acid, which was found to markedly contribute to the clinical symptoms observed in diarrheic calves.[12] There does not appear to be any hard evidence in favor or against the use of antimotility drugs in diarrheic animals. Their use is nonetheless discouraged based on the possible negative effects that certainly outweigh the subjective perception of clinical improvement that is based on the apparent reduction of feces production.[32,35]

Intestinal Protectants

Intestinal protectants such as kaolin and pectin are in general use for diarrheic animals; however, as with antimotility drugs, their value is uncertain. When they are used, the feces become bulky, but intestinal protectants do not have any known effect on the pathogenesis of the disease.

Alteration of the Diet

Whether or not diarrheic newborn animals should be deprived of milk during the period of diarrhea is under controversial debate. Diarrheic piglets are usually treated with an antimicrobial orally and left to nurse on the sow. Diarrheic beef calves are commonly treated with oral fluids and electrolytes and left with the cow. However, in dairy calves it is a common practice to reduce the milk intake of diarrheic animals for up to 24 hours or until there is clinical evidence of improvement. The withholding of milk from diarrheic calves has been advocated based on the consideration that lactose digestion is impaired and that "resting" the intestine for a few days will consequently minimize

additional osmotic diarrhea caused by fermentation of undigested lactose in the large intestine. In contrast, the argument in favor of continuous feeding of milk is that the intestinal tract requires a constant source of nutrition, which it receives from the ingesta in the lumen of the intestine. To date, there is no scientific evidence available confirming that transiently starving diarrheic animals has any beneficial effects on the clinical outcome. Studies exploring the effect of continuous milk feeding in diarrheic calves failed to confirm any deleterious effect, such as prolonged morbidity time, higher mortality rate, or higher treatment frequency. To the contrary, calves kept on milk had higher weight gains during the period of reconvalescence.[32,36] Although diarrheic animals clearly should be supplemented with oral electrolyte solutions to assist the compensation of excessive fluid and electrolyte loss, the currently available evidence is clearly in favor of maintaining the animal on milk or milk replacer. Calves should be offered reduced quantities of whole milk per feeding with higher feeding frequency. Milk should not be diluted with water because this may interfere with the clotting mechanism in the abomasum. In contrast to oral electrolyte solutions, milk should not be force-fed with an esophageal tube feeder because this will prevent closure of the reticular groove and thus foster accumulation of milk in the rumen, where it would be subject to bacterial fermentation.

Probiotics

The use of so-called probiotics for treatment and prevention of diarrhea has become increasingly popular over the past decades. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the health of the host.[37] Most probiotics intended for veterinary use belong to the broad class of lactic acid bacteria, which include *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Streptococcus* spp. Probiotics have been claimed to promote gastrointestinal health and immunity, to reduce the shedding of potential pathogens in feces, and to reduce the need for therapeutic intervention.[38] Most importantly, probiotics are widely considered not to be present any health risk for the patient. Unfortunately, to date there are no published clinical data obtained in animals supporting any of these claims. Of particular concern is that the use of probiotics in humans has been associated with *Lactobacillus* bacteremia in several immunocompromised patients, and deleterious effects with some commercial products have been observed in neonatal foals.[39] In veterinary medicine concerns have been voiced about the uncritical use of probiotics, particularly in neonates with systemic disease or with a compromised intestinal mucosa.[40,41] With the current knowledge, the use of probiotics cannot be recommended for treatment or prevention of neonatal diarrhea.

Clinical Management of Outbreaks

Veterinarians should consider the following principles when outbreaks of colibacillosis in neonatal farm animals are encountered:

- Visit the farm and conduct an epidemiologic investigation to identify risk factors.
- Examine each risk factor and how it can be minimized.
- Examine affected animals.
- Identify and isolate all affected animals if possible.
- Treat all affected animals as necessary.
- Take laboratory samples from affected and normal animals.
- Make recommendations for the control of diarrhea in animals to be born in the near future.
- Prepare and submit a report to the owner describing the clinical and laboratory results and how the disease can be prevented in the future.

TREATMENT

Calf enterotoxic colibacillosis

Fluid therapy (highest priority)

Parenteral fluid therapy to correct acid–base and water and electrolyte imbalances* (R-1)
Oral rehydration solution* (R-1)

Antimicrobial therapy

Amoxicillin (10 mg/kg IM/PO every 12h for at least 3 days) (R-2)
Amoxicillin-clavulanate (12 mg combined/kg PO/IM every 12h for at least 3 days) (R-2)
Ampicillin (10 mg/kg PO/IM every 12h for at least 3 days) (R-2)
Colistin (100,000 IU/kg PO every 24h for at least 3 days) (R-2)
Enrofloxacin (2.5 to 5 mg/kg IV/IM/SC/PO every 24h for at least 3 days) (R-2)
Neomycin (10 mg/kg PO q12h) (R-2)
Trimethoprim-sulfonamide (25 mg combined/kg IV/IM/PO every 12h for at least 3 days (R-2)

Antiphlogistic therapy

Flunixin meglumine (2.2 mg/kg IV once) (R-2)
Ketoprofen (6 mg/kg IM once) (R-2)
Meloxicam (0.5 mg/kg IV/SC once) (R-2)

Antimotility drugs (R-3)

Probiotics (R-3)

Calf septicemic colibacillosis

Antimicrobial therapy

Amoxicillin-clavulanate (25 mg/kg IV/IM every 6–8h) (R-2)
Ampicillin-sodium (10 mg/kg IV/IM every 8h) (R-2)
Cefquinome (2 mg/kg IM every 24h) (R-2)
Ceftiofur (2.2 mg/kg IM/SC every 12 h) (R-2)
Enrofloxacin (5 mg/kg IV/IM every 24 h) (R-2)
Florfenicol (20 mg/kg IM every 24h) (R-2)
Trimethoprim-sulfonamide (25 mg combined/kg IV every 8–12h) (R-2)

Piglet enterotoxic colibacillosis

Fluid therapy (highest priority)

Oral rehydration solution* (R-1)
Amoxicillin (10 mg/kg PO/IM every 12h for at least 3 days) (R-2)
Amoxicillin-clavulanate (12 mg combined/kg PO/IM every 12h for at least 3 days) (R-2)
Ampicillin (10 mg/kg PO/IM every 12h for at least 3 days) (R-2)
Ceftiofur (1.1 to 2.2 mg/kg IM every 24h for at least 3 days) (R-2)
Chlortetracycline (20 mg/kg PO every 24h for at least 3 days) (R-2)
Enrofloxacin (2.5 to 5 mg/kg IV/IM/SC/PO every 24h for at least 3 days) (R-2)
Colistin (100,000 IU/kg PO every 24h for at least 3 days) (R-2)
Oxytetracycline (10 mg/kg IM every 24h for at least 3 days) (R-2)
Neomycin (10 mg/kg PO every 12h for at least 3 days) (R-2)
Trimethoprim-sulfonamide (25 mg combined/kg IV/IM/PO every 12h for at least 3 days (R-2)

**See "Principles of Fluid and Electrolyte Therapy."*

CONTROL

Because of the complex nature of the disease, it is unrealistic to expect total prevention, and control at an economical level should be the major goal. Effective control of colibacillosis can be accomplished by the application of three principles:

- Reduce the degree of exposure of the newborn to the infectious agents.
- Provide maximum nonspecific resistance with adequate colostrum and optimum animal management.
- Increase the specific resistance of the newborn by vaccination of the dam or the newborn.

Reduction of the Degree of Exposure of the Newborn to the Infectious Agents

The emphasis is on ensuring that newborns are born into a clean environment. Barns, confinement pens, and paddocks used as parturition areas must be clean and should preferably have been left vacant for several days before the pregnant dams are placed in them.

Dairy Calves

The following comments are directed particularly at calves born indoors, where contamination is higher than outdoors:

- Greatest attention must be paid to maternity pen hygiene. Calves should be born in well-bedded clean and dry box stalls.
- Obstetric intervention and assistance to calving should be provided by adequately trained personnel in a calm and hygienic manner.

- Immediately after birth the umbilicus of the calf should be swabbed or dipped 2% iodine tincture or chlorhexidine solution.
- In herds with high disease incidence the residence time of calves in the maternity pen should be kept as short as possible and calves moved to clean, dry, and well-bedded individual calf pens or hutches as soon as possible after birth.
- Calves affected with diarrhea should be removed from the main calf barn if possible and treated in isolation.

Beef Calves

Beef calves are usually born on pasture or on confined calving grounds, and the following guidelines apply:

- Calving grounds should have been free of animals previous to the calving period; the grounds should be well drained, dry, and scraped free of snow if possible. Each cow–calf pair should be provided with at least 2000 sq ft of space. Calving on pasture with adequate protection from wind is ideal. Covering the calving grounds with straw or wood shavings provides a comfortable calving environment.
- In large beef herds, in a few days following birth when the calf is nursing successfully, the cow–calf pair should be moved to a nursery pasture to avoid overcrowding in the calving grounds.

In beef herds, breeding plans should ensure that heifers calve at least 2 weeks before the mature cows. Limiting the breeding and therefore the calving season to 45 days or less for heifers also offers several advantages. A short calving season allows the producer to more effectively and economically concentrate personnel resources on calving management compared with a longer calving season. Calving heifers earlier allows them additional time required before the next breeding season to be on an increasing plane of nutrition necessary to maintain a high conception rate. The earlier calving of heifers also provides less exposure of their calves to infection pressure from the mature animals in the herd.

The incidence and severity of neonatal disease will typically increase, and the age at disease onset will decrease, as the calving season progresses. This phenomenon is common in beef herds because of the effect of the calf as a biological amplifier. The more the calving season is shortened, the more the biological amplification effect is negated.

For beef herds, it is necessary to have a plan for cattle movement throughout the calving season. This requires a minimum of four or five separate pastures: a gestation pasture, a calving pasture, and a series of nursery pastures. To ensure that beef calves are born in a sanitary environment, the herd should be moved from the gestation pasture to the calving pasture 1 to 2 weeks before calving. One day after birth, the cow or heifer and her calf should be moved to a nursery pasture. Cow–calf pairs should be added to a single nursery pasture until the appropriate number of pairs has been reached. Thereafter, cow–calf pairs can be added to a second nursery pasture. The difference in age between the oldest and youngest calf in a nursery pasture should never exceed 30 days, and smaller differences are preferable. This negates the biological amplification effect. The longer the calving season, the greater the need for a large number of nursery pastures. Calves that develop diarrhea should be removed immediately to an area away from healthy calves, treated, and not returned until all calves in the group are at low risk for developing diarrhea (>30 days of age).

The nutrition of the pregnant cows, and particularly the first-calf heifers, must be monitored throughout gestation to ensure an adequate body condition and sufficient resources to provide an adequate supply of good-quality colostrum.

Veal Calves

Veal calves are usually obtained from several different sources, and 25% to 30% or higher may be deficient in serum immunoglobulin. The following guidelines apply to veal calves:

- On arrival, calves should be placed in their individual calf pens, which were previously cleaned, disinfected, and left vacant to dry.
- Feeding utensils are a frequent source of pathogenic *E. coli* and should be cleaned and air-dried daily.
- Calves affected with diarrhea should be removed and isolated immediately.

Lambs and Kids

The principles described earlier for calves apply to lambs and kids. Lambing sheds can be a source of heavy contamination and must be managed accordingly to reduce infection pressure on newborn lambs.

Piglets

Piglets born in a total-confinement system may be exposed to a high infection rate. The following guidelines apply to piglets:

- The all-in/all-out system of batch farrowing, in which groups of sows farrow within a week, is recommended. This system will allow the herdsman to wean the piglets from a group of sows in a day or two and clean, disinfect, and leave vacant a battery of farrowing crates for the next group of sows. This system will reduce the total occupation time and the infection rate. The continuous farrowing system without regular breaks is not recommended.
- Before being placed in the farrowing crate, sows should be washed with a suitable disinfectant to reduce the bacterial population of the skin.

Provision of Maximum Nonspecific Resistance With Adequate Colostrum and Optimum Animal Management

The first step of fostering maximum nonspecific resistance is the provision of optimal nutrition to the pregnant dam, which will result in a vigorous newborn animal and adequate quantities of colostrum. At the time of parturition, surveillance of the dams and the provision of any obstetric assistance required will ensure that newborns are born with as much vigor as possible. Parturition injuries and intrapartum hypoxemia must be minimized as much as possible.

Colostrum Management

The next most important control measure is to ensure that liberal quantities of good-quality colostrum are available and ingested within minutes and no later than a few hours after birth. Although the optimum amount of colostrum that should be ingested by a certain time after birth is well known, the major difficulty with all species under practical conditions is to know how much colostrum a particular neonate has ingested. Because modern livestock production has become so intensive, it is imperative that the animal attendants make every effort to ensure that sufficient colostrum is ingested by that particular species. In a recent national survey in the United States, the estimated prevalence of failure of passive immunity transfer in female dairy calves was 19.2%.[41]

Failure of transfer of passive immunity (FTPI), as determined by calf serum immunoglobulin IgG_1 concentration below 1000 mg/dL at 48 hours of age, occurred in 61.4% of calves from a dairy in which calves were nursed by their dams, 19.3% of calves from a dairy using nipple bottle feeding, and 10.8% of calves from a dairy using tube feeding. A higher prevalence of FTPI in dairy calves can occur because an insufficient volume of colostrum is ingested by the calf. When artificial feeding is used, inadequate immunoglobulin concentration in the colostrum fed is the most important factor resulting in FTPI. The prevalence of FTPI in dairy herds can be minimized by artificially feeding all newborn calves large volumes (3 to 4 L) of fresh or refrigerated first-milking colostrum from cows that had nonlactating intervals of normal duration. This volume is considerably greater than the intake that Holstein calves usually achieve by sucking and also exceeds the voluntary intake of most calves fed colostrum by nipple bottle.

Calves need to ingest at least 100 g of IgG_1 in the first colostrum feeding to ensure adequate transfer of passive immunity. Thus the routine force-feeding of a sufficient amount of pooled colostrum immediately after birth results in high serum levels of colostrum immunoglobulin in dairy calves and is becoming a common practice in dairy herds.

Encouraging and assisting the calf to suck within 1 hour after birth is also effective. The

provision of early assisted sucking of colostrum to satiation within 1 hour after birth will result in high concentrations of absorbed immunoglobulin in the majority of calves. The ingestion of 100 g or more of colostral immunoglobulin within a few hours after birth is more effective in achieving high levels of colostral immunoglobulin in calves than either leaving the calf with the cow for the next 12 to 24 hours or encouraging the calf to suck again at 12 hours, which will not result in a significant increase in absorbed immunoglobulin.

Despite early assisted sucking, a small proportion of calves will remain hypogammaglobulinemic because of low concentrations of immunoglobulin in their dams' colostrum, usually associated with leakage of colostrum from the udder before calving.

In large herds where economics permit, a laboratory surveillance system may be used on batches of calves to determine the serum levels of immunoglobulin acquired. An accurate analysis may be done by electrophoresis or an estimation using the zinc sulfate turbidity test. Blood should be collected from calves at 24 hours of age. Samples taken a few days later may not be a true reflection of the original serum immunoglobulin concentrations. The information obtained from determination of serum immunoglobulin in calves at 24 hours of age can be used to improve management practices, particularly the early ingestion of colostrum.

Quality of Colostrum

Specific Gravity

Differentiating high-immunoglobulin-concentration colostrum from low-immunoglobulin-concentration is problematic. Measurement of the specific gravity of the colostrum of dairy cows with a commercially available hydrometer (Colostrometer) has been explored. Originally it was claimed that measurement of specific gravity provided an inexpensive and practical method for estimating colostral immunoglobulin concentration. However, the specific gravity of colostrum is more correlated with its protein concentration than immunoglobulin concentration and varies with colostral temperature, thus limiting the predictive accuracy of the test. In addition, different relationships between specific gravity and immunoglobulin concentration of colostrum have been observed for different populations of Holstein Friesian and Jersey cows and between herds. Specific gravity may also vary considerably according to season of the year. Specific gravity was measured in 1085 first-milking colostrum samples from 608 dairy cows of four breeds on a single farm during a 5-year period. The specific gravity more closely reflected protein concentration than IgG concentration and was markedly affected by month of calving. Colostral specific gravity values were highest for Holstein and Jersey cows, cows in third or later lactation, and cows calving in autumn. They were lowest in Brown Swiss and Ayrshire cows, cows in first or second lactation, and cows calving in summer. Thus using the specific gravity of colostrum as an indicator of IgG concentration has potential limitations.

Frozen and Thawed Colostrum

Colostrum can be banked as frozen colostrum for future use. Excess colostrum can be stored frozen and thawed as necessary to provide an IgG source when administration of dam colostrum is impractical or insufficient. Experience has shown that the composition of frozen colostrum remains constant throughout storage. No significant changes in pH, percentage acidity, milk fat, total solids, total nitrogen, or nonprotein resulted from colostrum being stored. Feeding 4 L of frozen thawed colostrum (which had been frozen at −20° C (−4° F) for 24 h) to calves by orogastric tube at 3 hours after birth did not result in a significant difference in IgG absorption compared with calves receiving fresh colostrum.

Pasteurization of Colostrum

There are several indications for pasteurization of colostrum. This procedure can be a suitable instrument in a program for the control of specific infectious diseases, such as paratuberculosis, salmonellosis, or *M. bovis* infection, but it can also be useful to ameliorate calf health by improving colostrum quality and reducing the exposure of the neonate to pathogens. On-farm pasteurization of bovine colostrum for 60 min at 60° C (140° F) results in elimination or at least significant reduction of bacterial contamination without impairing fluid characteristics or availability of IgG for intestinal absorption.[7] One recent study reported significantly higher serum IgG concentrations at 24 hours of life when calves were fed pasteurized colostrum compared with calves receiving the same quality and amount of raw colostrum.[42] The authors attributed this effect to reduced bacterial interference with intestinal IgG absorption. Pasteurization extends the shelf life of refrigerated colostrum without additives to 8 to 10 days when stored in clean, sealed containers.

Colostrum Supplements and Replacers

Some colostrum-derived oral supplements containing immunoglobulin are available for newborn calves in which colostrum intake is suspected or known to be inadequate. **Colostrum supplement** products have been developed to provide exogenous IgG to calves when the dam's fresh colostrum is of low IgG concentration. Many producers also use these products to replace colostrum when it is unavailable as a result of maternal agalactia, acute mastitis, or other causes of inadequate colostrum supply. However, they contain low immunoglobulin concentrations compared with those found in high-quality first-milking colostrum. Most colostral supplements provide only 25 to 45 g of IgG/dose of 454 g, which is reconstituted in 2 L of water. Feeding one or even two doses of such supplements is insufficient to provide a mass of 100 g of IgG within the first 12 hours after birth. **Colostrum replacers** are intended to provide the sole source of IgG and thus must provide at least 100 g of IgG. Newborn colostrum-deprived dairy calves fed spray-dried colostrum containing 126 g of immunoglobulin in 3 L of water as their sole source of immunoglobulin achieved normal mean serum immunoglobulin concentrations. Whey protein concentrate as a colostrum substitute, administered to calves as a single feeding, was ineffective in preventing neonatal morbidity and mortality compared with a single feeding of pooled colostrum.

The IgG derived from bovine serum or immunoglobulin concentrates from bovine plasma are well absorbed by neonatal calves when given in adequate amounts. The serum concentration of IgG in calves at 2 days of age force-fed a colostrum supplement containing spray-dried serum (total of 90 g immunoglobulin protein) within 3 hours after birth was much lower than in calves fed 4 L of fresh colostrum. The mass of IgG and the method of processing are critical. Products providing less than 100 g of IgG/dose should not be used to replace colostrum.

To be successful, colostral supplements and replacers must provide enough IgG mass to result in 24-hour calf serum IgG concentrations of more than 10 g/L.

Purified Bovine Immunoglobulin

The administration of purified bovine gammaglobulin to calves that are deficient appears to be a logical approach, but the results have been unsuccessful. Large doses (30 to 50 g) of gammaglobulin given intravenously would be required to increase the level of serum gammaglobulin from 0.5 g/dL to 1.5 g/dL of serum, which is considered an adequate level. The cost would be prohibitive. The administration of gammaglobulin by any parenteral route other than the intravenous route does not result in a significant increase in serum levels of the immunoglobulin.

To be effective, infusion of immunoglobulin derived from blood must increase serum IgG concentrations and reduce morbidity and mortality before weaning without affecting later production. Parenteral infusions of immunoglobulin will increase the concentrations of serum IgG in calves, but may not necessarily have an effect on morbidity or mortality. High levels of specific circulating immunoglobulin can serve as a reservoir of antibodies to move into the intestine and prevent enteric infection. Thus immunoglobulin sources other than colostrum may not provide immunoglobulins that are specific for antigens present in the environment

or might be insufficient when calves are exposed to a heavy infection pressure.

Beef Calves

The management strategies to decrease calf death losses in beef herds have been described. The role of management intervention in the prevention of neonatal deaths includes measures to improve host defenses and environmental hygiene to minimize outbreaks of neonatal disease. Specific attention is centered on preventing dystocia, improving transfer of colostral immunoglobulin, and limiting environmental contamination.

The following practices should be implemented:

- Management of the beef herd must emphasize prevention of dystocia, which involves limiting calf size and ensuring adequate pelvic area of the dams.
- Beef calves should be assisted at birth, if necessary, to avoid exhaustion and weakness from a prolonged parturition.
- Normally beef calves will make attempts to get up and suck within 20 minutes after birth, but this may be delayed for up to 8 hours or longer. Beef calves that do not suck within 2 hours should be fed colostrum by nipple bottle or stomach tube. Whenever possible, they should be encouraged and assisted to suck to satiation within 1 hour after birth. The dam can be restrained and the calf assisted to suck. If the calf is unable or unwilling to suck, the dam should be restrained and milked out by hand, and the calf should be fed the colostrum with a nipple bottle or stomach tube. The mean volume of colostrum and colostral immunoglobulin produced in beef cows and the absorption of colostral immunoglobulin by their calves can vary widely. Beef calves deserted by indifferent dams need special attention. FTPI is common and estimated at 10% to 40% of beef calves.
- Constant surveillance of the calving grounds is necessary to avoid overcrowding, to detect diarrheic calves that should be removed, to avoid mismothering, and to ensure that every calf is seen to nurse its dam. Although up to 25% of beef calves may not have sufficient serum levels of immunoglobulin, the provision of excellent management will minimize the incidence of colibacillosis. The recently developed practice of corticosteroid-induced parturition in cattle may result in a major mismothering problem if too many calves are born too quickly in a confined space. Every management effort must be used to establish the cow–calf herd as soon as possible after birth. This will require high-quality management to reduce the infection rate even further and minimize any stressors in the environment.

Lambs

Lambs require 180 to 210 mL of colostrum/kg BW during the first 18 hours after birth to provide sufficient energy for heat production. Such an intake will usually also provide enough colostral immunoglobulin. Early encouragement and assistance of the lambs to suck the ewe is important. Well-fed ewes usually have sufficient colostrum for singletons or twins. Underfed ewes may not have sufficient colostrum for one or more lambs, and supplementation from stored colostrum obtained by milking other high-producing ewes is a useful practice.

Piglets

The following practices should be implemented for piglets:

- Every possible economical effort must be made to ensure that each newborn piglet obtains a liberal supply of colostrum within minutes of birth. The farrowing floor must be well drained, and it must be slip-proof to allow the piglets to move easily to the sow's udder. Some herdsmen provide assistance at farrowing, drying off every piglet as it is born and placing it immediately onto a teat.
- The washing of the sow's udder immediately before farrowing with warm water and soap will reduce the bacterial population and may provide relief in cases of congested and edematous udders.
- The piglet creep area must be dry, appropriately heated for the first week, and free from drafts. During farrowing, colostrum is released in discrete ejections, possibly by discrete release of oxytocin associated with parturition. Therefore, as the piglets are born they must be as close to the udder as possible to take advantage of these discrete ejections.

Increasing Specific Resistance of the Newborn by Vaccinating the Pregnant Dam or the Newborn

The immunization of neonate farm animals against colibacillosis by vaccination of the pregnant dam or by vaccination of the fetus or the neonate has received considerable research attention in recent years, and the results appear promising.

Such vaccines are practical and effective for the following reasons:

- Most fatal ETEC infections in farm animals occur in the early neonatal period when antibody titers in colostrum and milk are highest.
- More than 90% of the ETEC in farm animals belong to a small family of fimbrial antigens.
- Fimbriae consist of good protein antigens on the bacterial surface, where they are readily accessible to antibodies.
- Fimbriae are required for a critical step (adhesion–colonization) early in the pathogenesis of the disease.
- Novel or previously low-prevalence fimbrial antigens have not emerged to render the vaccines ineffective.

The pregnant dam is vaccinated 2 to 4 weeks before parturition to induce specific antibodies to particular strains of enteropathogenic *E. coli*, and the antibodies are then passed on to the newborn through the colostrum. The mechanism of protection is the production of antibodies against the pilus antigens, which are responsible for colonization of *E. coli* in the intestine.

Vaccination is an aid to good management and not a replacement for good management practices. Vaccines to prevent ETEC diarrhea in calves and piglets are based on the prevailing fimbrial antigens for colonization by ETEC in calves (F5) and newborn pigs (F4, F5, and F6). Reliable data on the efficacy of the commercial vaccines based on randomized clinical field trials are not available, but most animal health professionals perceive that the vaccines are effective and that disease occurs primarily in unvaccinated herds. There are unpublished anecdotal reports that use of the vaccine in cattle has shifted the peak occurrence of diarrhea in calves from the first week to the third and fourth week after birth. The extensive use of fimbria-based vaccines can select against the prevailing fimbrial antigen types as reflected in the vaccines, and emergence of new or previously low-prevalence fimbrial antigens may occur. Fimbriae antigenically distinct from F1, F4, F6, F41 occur among ETEC. However, these antigen types are less prevalent than those currently used in commercial vaccines. There is no evidence that ETEC with novel colonization mechanisms or new fimbrial antigens have emerged under the selection pressure of vaccination. Nor is there evidence that previously "low-prevalence" fimbrial antigen types of ETEC, not represented in the vaccines, have emerged as "common pathogens" filling an ecological niche left by the fimbrial antigen types targeted by the vaccines.

Calves

Vaccination of pregnant cattle with either purified *E. coli* F5 (K99) pili or a whole-cell preparation containing sufficient F5 antigen can significantly reduce the incidence of enterotoxigenic colibacillosis in calves. Good protection is also possible when the dams are vaccinated with a four-strain *E. coli* whole-cell bacterin containing sufficient F5 pilus antigen and the polysaccharide capsular K antigen. Colostral antibodies specific for F5 pilus antigen and the polysaccharide capsular K antigen on the surface of the challenge exposure strain of ETEC are protective. There is a highly significant correlation

between lacteal immunity to the F5 antigen and the prevention of severe diarrhea or death in calves challenged with enterotoxigenic *E. coli*. The colostral levels of F5 antibody are highest during the first 2 days after parturition, which is the most susceptible period for enterotoxigenic colibacillosis to occur in the newborn calf. The continuous presence of the F5 antibody in the lumen of the intestine prevents adherence of the bacteria to the intestinal epithelium. The F5 antibody is also absorbed during the period of immunoglobulin absorption and may be excreted into the intestine during diarrhea. This may be one of the reasons that mortality is inversely proportional to serum immunoglobulin levels. The pregnant dams are vaccinated twice in the first year, 6 and 2 weeks before parturition. Each year thereafter they are given a single booster vaccination. An oil-emulsion *E. coli* F5 bacterin given once or twice to pregnant beef cows 6 weeks before calving elicited high levels of serum antibodies that provided protection against experimental infection of newborn calves for up to 87 weeks after vaccination.

Vaccines containing both the F5 antigen of ETEC and rotavirus, and in some cases coronavirus, have been evaluated, with variable results. The colostral antibodies to the F5 antigen are higher in vaccinated than unvaccinated dams, but the colostral antibodies to rotavirus and coronavirus may not be significantly different between vaccinated and unvaccinated dams. In these field trials vaccination had no effect on the prevalence of diarrhea, calf mortality, or the presence of the three enteropathogens. In other field trials the combined vaccine did provide some protection against outbreaks of calf diarrhea. The use of an inactivated oil-adjuvanted rotavirus *E. coli* vaccine given to beef cows in the last trimester of pregnancy decreases the mortality from diarrhea and has a positive influence on the average weight gains of the calves at weaning. To be effective the rotavirus and coronavirus antibodies must be present in the postcolostral milk for several days after parturition, during the period when calves are most susceptible to the viral infection. Vaccination of pregnant cows twice during the dry period at intervals of 4 weeks can increase the colostral antibody levels to *E. coli* F5 by 26 times on day 1 compared with controls. Much lower increases occur at the levels of coronavirus and rotavirus.

A commercially inactivated vaccine containing bovine rotavirus (serotype G6 P5), bovine coronavirus (originally isolated from a calf with diarrhea), and purified cell-free *E. coli* F5 (adsorbed on to aluminum hydroxide gel), formulated as an emulsion in a light mineral oil, has been evaluated in a herd of Ayrshire/Friesian cows vaccinated once at 31 days before the first expected calving date. Compared with control cows, a significant increase in the mean specific antibody titer against all three antigens occurred in the serum of vaccinated animals (even in the presence of preexisting antibodies), which was accompanied by increased levels of protective antibodies to rotavirus, coronavirus, and *E. coli* F5 in their colostrum and milk for at least 28 days.

Because naturally acquired antibodies to the **J5 antigen** may have an important role in the control of neonatal disease caused by bacterial infections with associated pathogens that share antigens with *E. coli* (J5 strain), vaccination of calves with an *E. coli* O111:B4(J5) vaccine at 1 to 3 days of age and 2 weeks later has been evaluated to control morbidity and mortality in dairy calves up to 60 days of age. The use of either a killed *E. coli* O111:B4(J5) bacterin or a modified live, genetically altered (aro-) *Salmonella dublin* vaccine, or both, in neonatal calves was effective in reducing mortality resulting from colibacillosis and salmonellosis. Such a vaccine may be beneficial in controlling mortality in well-managed herds, but it is contraindicated in poorly managed herds.

Passive immunotherapy of calves under 2 days of age with J5 *E. coli* hyperimmune plasma given subcutaneously at a dose of 5 mL/kg BW has been examined. The plasma was found to be safe and potent. It was not superior to control plasma or to no treatment for calf morbidity and mortality.

The oral administration of a F5-specific monoclonal antibody to calves during the first 12 hours after birth may be an effective method of reducing the incidence of fatal enterotoxigenic colibacillosis, particularly when outbreaks of the disease occur in unvaccinated herds. Clinical trials indicate that the severity of dehydration, depression, and weight loss and the duration of diarrhea were significantly reduced in calves that had received the F5-specific monoclonal antibody. In experimentally challenged calves the mortality was 29% in the treated calves and 82% in the control calves.

The decision to vaccinate in any particular year will depend on the recognition of risk factors. Such risk factors include the following:

- A definitive diagnosis of ETEC F5 in the previous year
- A population density in the calving grounds that is conducive to the disease
- Calving during the year when the environmental conditions are wet and uncomfortable for the calves
- A large percentage of primiparous dams that do not have protective levels of F5 antibody in their colostrum

Piglets

Piglets born from gilts are more susceptible than those from mature sows, which suggests that immunity improves with parity. On a practical basis this suggests that gilts should be mixed with older sows that have been resident on the premises for some time. The length of time required for such natural immunization to occur is uncertain, but 1 month during late gestation seems logical.

Naturally occurring enteric colibacillosis in newborn piglets can be effectively controlled by vaccination of the pregnant dam. Field trials in large-scale farm conditions indicate that the vaccines are efficacious. Partial budget analysis of vaccinating pregnant sows with *E. coli* vaccines revealed an economic return on investment of 124% because of the decrease in morbidity and mortality resulting from diarrhea in piglets at 1 to 2 weeks of age. Three antigen types of pili, designated F4, F5, and F6, are now implicated in colonization of the small intestine of newborn piglets by ETEC. The vaccination of pregnant sows with oral or parenteral vaccines containing these antigens will provide protection against enterotoxigenic colibacillosis associated with *E. coli* bearing pili homologous to those in the vaccines. The parenteral vaccines are cell-free preparations of pili, and the oral vaccines contain live enteropathogenic *E. coli*. The oral vaccine is given 2 weeks before farrowing and is administered in the feed daily for 3 days as 200 mL per day of a broth culture containing 10^{11} *E. coli*. A simple and effective method of immunization of pregnant sows is to feed live cultures of ETEC isolated from piglets affected with neonatal colibacillosis on the same farm. The oral vaccine can be given in the feed, beginning about 8 weeks after breeding and continued to parturition. The oral vaccine results in the stimulation of IgA antibody in the intestinal tract, which is then transferred to the mammary gland and into the colostrum. A combination of oral and parenteral vaccination is superior to either route alone. The parenteral vaccine is given about 2 weeks after breeding and repeated 2 to 4 weeks before parturition. The parenteral vaccination results in the production of high levels of IgM antibody for protection against both experimental and naturally occurring enterotoxigenic colibacillosis. This vaccination also reduces the number of *E. coli* excreted in the feces of vaccinated sows, which are major sources of the organism. Immunization of pregnant sows with an *E. coli* bacterin enriched with the F4 antigen results in the secretion of milk capable of preventing adhesion of F4 *E. coli* to the gut for at least 5 weeks after birth, at which time the piglet becomes naturally resistant to adhesion by the organism.

The possibility of selecting and breeding pigs that may be genetically resistant to the disease is being explored. The highest incidence of diarrhea occurs in progeny of resistant dams sired by susceptible sires. The homozygous dominants (SS) and the heterozygotes (Ss) possess the receptor and are susceptible, whereas it is absent in the homozygous recessives (ss) and the pigs are resistant. Sows that are genetically resistant may not be able to mount an immune response to the F4 antigen because of the inability of the organism to colonize the intestinal tract.

Competitive Exclusion Culture

An alternative method of control is the use of competitive exclusion cultures. The theory of competitive exclusion technology is to colonize the neonatal gastrointestinal tract with beneficial/commensal bacteria considered to be the normal flora of the healthy animals of a particular species. The mechanism of action is not known, but hypotheses include the following: exclusion of enteropathogens by competitive attachment sites and/or for nutrients; stimulation of the local immune mechanisms, which precludes colonization/invasion by enteric pathogens; and the production of various antimicrobial substances that either have direct action on pathogenic bacteria or produce conditions within the intestine that are unfavorable for the growth and colonization by pathogens. Experimentally, the oral administration of a porcine competitive exclusion culture to piglets within 12 hours after birth resulted in significant reductions in mortality, incidence of fecal shedding, and intestinal colonization by *E. coli* compared with control values. Mortality decreased from 23% in the control group to 2.7% in the treated group.

Lambs and Kids

Vaccination of pregnant ewes with F5 antigen will confer colostral immunity to lambs challenged with homologous ETEC. The pregnant ewes are vaccinated twice in the first year, at 8 to 10 weeks and 2 to 4 weeks before lambing; in the second year, one vaccination 2 to 4 weeks before lambing is adequate.

Immunization of pregnant goats has been used to stimulate the development of lacteal immunity against naturally occurring colibacillosis in kids. Vaccination of pregnant does 1 month before parturition with a subunit vaccine containing F4, F5, and F6 fimbrial antigens of *E. coli* and *C. perfringens* types B, C, and D toxins in an aluminum hydroxide adjuvant, along with improved management conditions, was highly successful in reducing neonatal morbidity and mortality resulting from diarrhea. Compared with two control groups, one in which no improvement in management was made and the second in which improvements were made without vaccination, in the vaccinated group with improved management conditions, neonatal morbidity and mortality were both reduced by a factor of 3 in group 1 and by factors of 9.5 and 12.5 in groups 2 and 3, respectively. Also, the duration of diarrhea was 3.7 and 12 times shorter in the kids of groups 2 and 3, respectively.

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WATERY MOUTH OF LAMBS (RATTLE BELLY, SLAVERS)

SYNOPSIS

Etiology Nonenteropathogenic *E. coli* endotoxemia predisposed by failure of passive transfer.

Epidemiology Higher risk with intensive housing with poor hygiene.

Clinical findings Loss of sucking reflex, retention of meconium or feces, excessive mucoid saliva, abomasal distension.

Lesions None specific.

Diagnostic confirmation Nothing pathognomonic.

Treatment Fluids and energy via stomach tube; antimicrobials.

Control Antimicrobials at birth, pen hygiene, ensure adequate colostral transfer.

ETIOLOGY

Watery mouth of lambs is thought to be the result of endotoxemia in young lambs. It is postulated that the neutral pH of the abomasum in newborn lambs coupled with low concentrations of colostral immunoglobulin in the gut allow rapid multiplication of nonenteropathogenic strains of *E. coli* in the gut, and to some extent systemically, which results in endotoxemia.

EPIDEMIOLOGY

Occurrence

The syndrome is primarily reported in lambs in Great Britain but has also been reported in New Zealand and in goat kids in Spain and North America. A related but perhaps separate entity, termed *salivary abomasum disease*, has been reported as common in 3- to 17-day-old lambs and kids in Greece.[1]

Animal and Environmental Risk Factors

Lambs 12 to 72 hours of age are affected. The disease is seen under all management systems, but it is rare in pastured flocks and occurs most commonly in lambs kept in intensive housing where there is poor hygiene of the lambing environment. Lambs from prolific ewes are at risk, and the disease is more common in triplets than twins or singles.

Delayed or poor colostral intake is a major risk factor, and situations that

predispose this may lead to outbreaks. A high prevalence has occurred in ram lambs castrated by the use of an elastic band at a very young age, and the resulting pain may have dissuaded them from feeding.

Other risk factors, all of which reduce sucking by the lamb, are inclement weather, mismothering, maternal agalactia, competition between twins or triplets, low vitality, and ewes in poor condition.

Experimental Disease

An equivalent clinical syndrome is reproducible by administering nonenterotoxic strains of *E. coli* by mouth to colostrum-deprived lambs, all of whom died within 24 hours.

Economic Importance

Watery mouth disease is a major cause of mortality of housed newborn lambs in Great Britain and is reported to be the cause of approximately 25% of all deaths of lambs in indoor intensive lambing systems. Where conditions allow, morbidity rates may approach 24%; without early treatment, case fatality rates are high.

PATHOGENESIS

Gram-negative bacteria, nonenterotoxigenic and nonenteropathogenic *E. coli*, in the environment are ingested as a result of a contaminated environment, or from a contaminated fleece, and survive passage through the neutral pH of the abomasum to be absorbed into the systemic circulation by the natural pinocytosis that occurs in the intestinal epithelium of newborn ruminants, producing endotoxemia.

CLINICAL FINDINGS

Affected lambs are normal at birth but become sick at 24 to 48 hours and up to 72 hours old. The disease is characterized by dullness, lethargy, a complete failure to suck, and excessive mucoid saliva around and drooling from the mouth. As the disease progresses there is hypothermia, failure to pass feces, cold extremities, depression to the point of coma, anorexia, and, in the late stages, abdominal distension and recumbency, but rarely diarrhea. The alimentary tract is full of fluid, and the lamb rattles when it is shaken. Some lambs are hypothermic, but the temperature is normal at the onset of the condition and falls to subnormal as the disease progresses. Progress is rapid, with death 6 to 24 hours after the first signs of illness. Salivary abomasum disease is reported in flocks that vaccinate against clostridial disease.[2]

CLINICAL PATHOLOGY

Total protein concentrations and base excess values are significantly elevated compared with normal lambs. Blood glucose concentrations are normal but may be low in the terminal phase of the disease.

NECROPSY FINDINGS

There are no findings specific to watery mouth syndrome. The abomasal contents are fluid and mucoid and contain small milk curds, and the intestine is filled with gas. A case series of lambs with salivary abomasum disease found pale kidneys and acute tubular necrosis in 90%. *E. coli* was cultured from only 6 of 37 abomasa in this study.[2]

TREATMENT

Treatment with intramuscular amoxillin and clavulanic acid, intravenous flunixin meglumine, and oral rehydration fluid, when administered early in the clinical course, has resulted in a high recovery rate in field cases. Dextrose solution should also be given to those lambs that are hypoglycemic, and external warming should be provided. Other recommended treatments include emptying the alimentary tract by purgation or enema.

DIFFERENTIAL DIAGNOSIS

Most neonatal disease of lambs is manifest with diarrhea, which is not present in watery mouth. The early stages of *Colisepticemia* and *Clostridium perfringens* type B or C present with similar clinical signs, but they are easily differentiated later in the clinical course or at postmortem examination. Hypothermia/starvation/cold stress can present with similar clinical findings, but the history and environmental circumstances of occurrence differ.

CONTROL

In outbreaks the administration of antibiotics to all newborn lambs within 15 minutes to 2 hours of birth dramatically reduces the occurrence of further cases. Fresh or frozen sheep or cow colostrum should be supplemented to lambs at risk. The provision of ewe colostrum at 50 mL/kg BW within 6 hours of birth prevents the disease.

Lambing areas and associated pens and yards should be kept clean and freshly bedded. Contaminated fleece should be removed from around the udder of the ewe before lambing, and every effort should be made to ensure early and adequate colostral intake by newborn lambs, especially for twins and triplets.

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OMPHALITIS, OMPHALOPHLEBITIS, AND URACHITIS IN NEWBORN FARM ANIMALS (NAVEL ILL)

Infection of the umbilicus and its associated structures occurs commonly in newborn farm animals and appears to be particularly common in calves. The umbilical cord consists of the amniotic membrane, the umbilical veins, the umbilical arteries, and the urachus. The amniotic membrane of the umbilical cord is torn at birth, and gradually the umbilical vein and the urachus close, but they remain temporarily outside the umbilicus. The umbilical arteries retract as far back as the top of the bladder.

In many countries regulations govern the minimal age at which neonatal calves can be shipped or sent to market and slaughter. The wetness or dryness of the umbilicus is used as a surrogate measure of age in welfare regulations, and the requirement is that the umbilical cord at the junction with the abdominal skin should be dry and shriveled. The drying time varies from 1 to 8 days, with variation between breeds and a longer drying period in bull calves. As might be expected, this measure is only an approximate surrogate for age, but approximately 90% of calves have dry navels by 4 days of age.[1]

Incidence of the disease is scarcely reported. The 30-day incidence of clinically apparent omphalitis in Thoroughbred foals in the United Kingdom was 0.7%, which was not reduced by administration of antimicrobials prophylactically.[2] Omphalitis was considered the cause of death in 23% of 247 calves 4 to 7 days of age that died during the preslaughter period (12 to 18 hours) at abattoirs in New Zealand.[1] The death rate was 0.7%, of which 23% was attributable to omphalitis. Omphalitis was the cause of wastage (condemnation of the carcass) in 54% of calves examined after slaughter.[1]

Infection of the umbilicus occurs **soon after birth** and can result in omphalitis, omphalophlebitis, omphaloarteritis, or infection of the urachus, with possible extension to the bladder, causing cystitis. There is usually a **mixed bacterial flora** including *E. coli*, *Proteus* spp., *Staphylococcus* spp., *T. pyogenes*, *Bacteroides* spp., *F. necrophorum*, and *Klebsiella* spp. The most common, and presumed clinically important, infections in foals are by *E. coli* and *S. zooepidemicus*. Infection of umbilical remnants in foals by *Clostridium sordelli* causes peritonitis, urachitis, omphalophlebitis, and omphaloarteritis.[3]

Bacteremia and localization with infection may occur in joints, bone, meninges, eyes, endocardium, and end-arteries of the feet, ears, and tail. The navel can also be the source of infection, leading to septicemia, arthritis, and fever of unknown origin in neonates with FTPI. The incidence of abnormalities of the umbilicus and consequent rate of umbilical infection is high in cloned calves.[2-5]

OMPHALITIS

Omphalitis is inflammation of the external aspects of the umbilicus and occurs commonly in calves and other species within 2 to 5 days of birth and often persists for several weeks. The umbilicus is enlarged, is painful on palpation, and can be closed or draining

purulent material through a small fistula. The affected umbilicus can become very large and cause subacute toxemia. The calf is moderately depressed, does not suck normally, and is febrile. Treatment consists of surgical exploration and excision. A temporary drainage channel may be necessary.

OMPHALOPHLEBITIS

Omphalophlebitis is inflammation of the umbilical veins. It can involve only the distal parts or extend from the umbilicus to the liver. Large abscesses can develop along the course of the umbilical vein and spread to the liver, with the development of a hepatic abscess that can occupy up to one-half of the liver. Affected foals and calves are usually 1 to 3 months of age and are unthrifty because of chronic toxemia. The umbilicus is usually enlarged with purulent material; however, in some cases the external portion of the umbilicus appears normal-sized. Placing the animal in dorsal recumbency and deep palpation of the abdomen dorsal to the umbilicus in the direction of the liver might reveal a space-occupying mass. **Ultrasonographic** examination, including measurement of the size of umbilical structures, allows detection of omphalophlebitis, including any extension along the vein to the liver.

Affected calves and foals are inactive, inappetent, and unthrifty and may have a mild fever. Parenteral therapy with antibiotics is not uniformly successful and may need to be administered for prolonged times. Exploratory laparotomy and **surgical removal** of the abscess is often necessary. Large hepatic abscesses are usually incurable unless surgically removed, but the provision of a drain to the exterior and daily irrigation may be attempted if resection is not feasible.

OMPHALOARTERITIS

In omphaloarteritis, which is less common, the abscesses occur along the course of the umbilical arteries from the umbilicus to the internal iliac arteries. The clinical findings are similar to those in omphalophlebitis: chronic toxemia, unthriftiness, and failure to respond to antibiotic therapy. An unusual presentation is that of distal aortic aneurysm secondary to ascending infection of the umbilical artery.[6] The affected foal was 3 months of age and was examined because of colic and frequent urination. Treatment of omphalophlebitis consists of surgical removal of the abscesses.

URACHITIS

Infection of the urachus may occur anywhere along the urachus, from the umbilicus to the bladder. The umbilicus is usually enlarged and draining purulent material, but it can appear normal. Deep palpation of the abdomen in a dorsocaudal direction from the umbilicus may reveal a space-occupying mass. Extension of the infection to the bladder can result in cystitis and pyuria.[5] **Contrast radiography** of the fistulous tract and the bladder will reveal the presence of the lesion. The treatment of choice is exploratory laparotomy and surgical removal of the abscesses. Recovery is usually uneventful.

CONTROL

The control of umbilical infection depends primarily on **good sanitation and hygiene** at the time of birth. The application of drying agents and residual disinfectants such as tincture of iodine is widely practiced. However, there is limited evidence that chemical disinfecting is of significant value. Chlorhexidine is more efficient in reducing the number of organisms than 2% iodine or 1% povidone iodine. High concentrations of iodine (7%) are most effective, but these are damaging to tissue and should not be used.

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NEONATAL STREPTOCOCCAL INFECTION

SYNOPSIS

Etiology Various *Streptococcus* spp.

Epidemiology Neonatal foals, calves, lambs, piglets.

Signs Acute painful swelling of joints, lameness, fever; signs of meningitis, omphalophlebitis, ophthalmitis; sudden death.

Clinical pathology Culture organism from joint fluid.

Necropsy findings Fibrinopurulent synovitis, purulent meningitis and omphalophlebitis.

Diagnostic confirmation Recovery of organism from joint fluid.

Differential diagnosis Other infectious causes of arthritis, meningitis, and omphalophlebitis.

Treatment Antimicrobials, usually penicillin.

Control See "Principles of Control and Prevention of Infectious Diseases of Newborn Farm Animals" in Chapter 3.

ETIOLOGY

Streptococci are an important cause of septicemia, polyarthritis, meningitis, polyserositis, endocarditis, and unexpected death in the neonates of all farm animal species. Meningitis associated with streptococcal infection is restricted to the neonate in all species except piglets, in which outbreaks can occur in pigs after weaning, and lambs infected with *S. suis*, in which meningitis can occur as a sporadic disease at 3 to 5 months of age. Historically, there are reports of isolates of most of the Lancefield groups of beta-hemolytic streptococci, of nonbeta-hemolytic streptococci, and of viridans group streptococci from neonatal disease in farm animals. Commensal skin streptococci can occasionally cause disease in presumably immunocompromised neonates. However, the majority of neonatal disease is associated with a limited number of streptococcal species, although there can be geographic variation in their relative prevalence within animal species.

In **foals,** *S. zooepidemicus* (*S. equi* subsp. *zooepidemicus*) is the most common streptococcal species recovered from septicemic disease and polyarthritis and is also a cause of placentitis and abortion in mares.[1,2] *S. equisimilis* (*S. dysgalactiae* subsp. *equisimilis*) is a less common isolate.[2]

S. suis and *S. equisimilis* are the most common species incriminated in **piglets**. *S. suis* is especially important and is presented separately in the next section. Other Lancefield groups have been associated with sporadic disease. In **calves**, *S. dysgalactiae* and *S. uberis* are the common streptococcal isolates from synovial fluid of neonatal calves with arthritis. Beta-hemolytic streptococci are isolated from approximately 16% of septicemic calves in South Africa.[3] *Streptococcus pluranimalium* infection is reported in a single premature calf.[4]

S. dysgalactiae is also reported to be the most common cause of outbreaks of arthritis in neonatal lambs in Great Britain. *Streptococcus bovis* biotype 1 is reported to cause meningoencephalitis in llama cria.[5] *Streptococcus agalactiae* causes periarticular abscesses in camel foals in Africa.[6]

Streptococci can also contribute to purulent infections at local sites, such as navel ill of all species or otitis media in neonatal calves, although the latter is more commonly caused by *M. bovis*.[7]

EPIDEMIOLOGY

Occurrence and Prevalence

The importance and relative prevalence of streptococcal infections in neonatal disease varies among countries and with surveys.

Streptococci are a common cause of postnatal infections of **foals,** representing 50% of such cases in some surveys, but with a lower prevalence in others. Up to 20% of abortions in mares are a result of placentitis from streptococcal infection. Streptococcal septicemia as a result of beta-hemolytic streptococci may occur in foals under 5 days of age that have been stressed and have FTPI.

In **calves**, neonatal infections with streptococci are usually sporadic and less common than infections with gram-negative bacteria and may be predisposed by FTPI. In **lambs**, *S. dysgalactiae* is associated with outbreaks with high morbidity, and in Great Britain *S. dysgalactiae* is reported to be the cause of over 70% of cases of polyarthritis in lambs during their first 3 weeks of life. Despite the

high attack rate in these outbreaks, it is rare for more than one of twins or triplets to have disease. Streptococcal arthritis associated with *S. suis* infection in piglets is a common disease and is covered in a separate section.

Source of Infection

The source of the infection is usually the environment, which may be contaminated by uterine discharges from infected dams or by discharges from lesions in other animals. *S. dysgalactiae* is reported to survive for up to a year on clean straw, as opposed to wood shavings, which do not support the persistence of the organism.

The portal of infection in most instances appears to be the umbilicus, and continued patency of the urachus is thought to be a contributing factor in that it delays healing of the navel. In piglets there can be high rates of infection associated with infection entering through skin abrasions such as carpal necrosis resulting from abrasive floors or facial lesions following fighting. Contaminated knives at castration and tail docking, or contaminated ear taggers, can result in infection and disease. Other mechanical vectors include the screwworm fly (*Cochliomyia americana*).

The organism can be isolated from the nasopharynx of the sow, and direct infection from the sow to the piglet is suggested by some epidemiologic data.

Economic Importance

Affected foals and other species may die or be worthless as working animals because of permanent injury to joints. There is also loss resulting from condemnation at slaughter.

Zoonotic Implications

S. zooepidemicus is associated with human infections,[8] particularly nephritis, and many human infections can be traced back to the consumption of contaminated animal food products. Some strains of *S. equisimilis* can also infect humans.

PATHOGENESIS

The infection spreads from the portal of entry to produce a bacteremia that is not detectable clinically. The period of bacteremia is variable but it may last several days in piglets. A terminal acute fatal septicemia is the common outcome in animals under 1 week of age; in older animals, suppurative localization in various organs is more common. Arthritis is the most common manifestation, with synovitis and invasion of medullary bone of the epiphysis with microabscessation and ischemic necrosis of bone. Other manifestations of infection include ophthalmitis in foals and calves, meningitis and endocarditis in piglets, meningitis in calves, and endocarditis and sudden death in lambs. Streptococcal endocarditis can be produced by the intravenous inoculation of group L *Streptococcus*. Lesions are well established within 5 days, the left heart is most commonly affected, and myocardial and renal infarction occur.

CLINICAL FINDINGS

Foals

The disease is one of septicemia, often with localization of infection in joints (septic arthritis) or an eye (hypopyon), and is described in detail under "Neonatal Infection" (page 1874). Infection of the umbilicus can cause omphalitis and omphalophlebitis.

Piglets

Arthritis and meningitis may occur alone or together and are most common in the 2- to 6-week age group. More commonly, several piglets within a litter are affected. The arthritis is identical to that previously described in foals. With meningitis there is a systemic reaction comprising fever, anorexia, and depression. The gait is stiff, the piglets stand on their toes, and there is swaying of the hindquarters. The ears are often retracted against the head. Blindness and gross muscular tremor develop, followed by inability to maintain balance, lateral recumbency, violent paddling, and death. In many cases there is little clinical evidence of omphalophlebitis. With endocarditis the young pigs are usually found comatose or dead, without premonitory signs having been observed.

Lambs

Lameness in one or more limbs of lambs up to 3 weeks of age is the common presenting sign of infection with *S. dysgalactiae*, but approximately 25% of lambs can be initially recumbent. With this infection there is not major joint swelling in the early stages, and myopathy or delayed swayback may be initial considerations. In contrast with outbreaks that occur following docking, the incubation period is short, usually 2 to 3 days, and there is intense lameness, with swelling of one or more joints appearing in a day or two. Pus accumulates, and the joint capsule often ruptures. Recovery usually occurs with little residual enlargement of the joints, although there may be occasional deaths as a result of toxemia.

Calves

Calves show polyarthritis, meningitis, ophthalmitis, and omphalophlebitis. The ophthalmitis may appear very soon after birth. The arthritis is often chronic and causes little systemic illness. Calves with meningitis show hyperesthesia, rigidity, and fever.

CLINICAL PATHOLOGY

Pus from any source may be cultured to determine the organism present and its sensitivity to the drugs available. Bacteriologic examination of the uterine discharges of the dam may be of value in determining the source of infection. The success rate with blood cultures is not very high, but an attempt is worthwhile. The identification of the causative bacteria is important, but the sensitivity of the organism may mean the difference between success and failure in treatment. The specific identity of the streptococcus should be determined.

NECROPSY FINDINGS

Suppuration at the navel and severe suppurative arthritis affecting one or more joints are usual. Abscesses may also be present in the liver, kidneys, spleen, and lungs. Friable tan masses of tissue are common on the heart valves of affected piglets, and this valvular endocarditis may also be observed in other species. Peracute cases may die without suppurative lesions having had time to develop. Necropsy findings in the meningitic form in pigs include turbidity of the CSF, congestion of meningeal vessels, and the accumulation of white, purulent material in the subarachnoid space. Occasionally this exudate blocks the flow of CSF in the ventricular system, causing internal hydrocephalus. Histologically there is infiltration of the affected tissue by large numbers of neutrophils, usually accompanied by fibrin deposition.

Samples for Confirmation of Diagnosis

Confirmation of diagnosis is made with the following samples:

- Bacteriology—culture swabs from joints, meninges, suppurative foci; tissue pieces of valvular lesions, lung, spleen, synovial membrane (culture)
- Histology—formalin-fixed samples of a variety of organs, including brain, lung, spleen, liver (light microscopy)

DIFFERENTIAL DIAGNOSIS

Omphalophlebitis and suppurative arthritis in foals may result from infection with *Escherichia coli, Actinobacillus equuli*, or *Salmonella abortusequi*, but these infections tend to take the form of a fatal septicemia within a few days of birth, whereas streptococcal infections are delayed in their onset and usually produce a form of polyarthritis. In pigs there may be sporadic cases of arthritis as a result of staphylococci, but the streptococcal infection is the common one. Arthritis as a result of *Mycoplasma hyorhinis* is less suppurative, but it may require cultural differentiation. Glasser's disease occurs usually in older pigs and is accompanied by pleurisy, pericarditis, and peritonitis. Erysipelas in very young pigs is usually manifested by septicemia. Nervous disease of piglets may resemble arthritis on cursory examination, but there is an absence of joint enlargement and lameness. However, the meningitic form of the streptococcal infection can easily be confused with viral encephalitides. Meningitis in young calves may also be associated with *Pasteurella multocida*. Polyarthritis in calves, lambs, and

piglets may also be associated with infection with *Trueperella pyogenes* and *Fusobacterium necrophorum*. *S. suis* type 2 can also be the cause of meningitis in older pigs at 10 to 14 weeks of age.

The response of streptococcal infections to treatment with penicillin may be of value in the differentiation of the arthritides, and the microscopic and histologic findings at necropsy enable exact differentiation to be made. In lambs, suppurative arthritis occurs soon after birth and after docking. The other common arthritis in the newborn lamb is that associated with *Erysipelothrix rhuriophiae*, but this usually occurs later and is manifested by lameness without pronounced joint enlargement. Calves may also develop erysipelatous arthritis.

TREATMENT

Penicillin is successful as treatment in all forms of the disease if irreparable structural damage has not occurred. In newborn animals, the dosage rate should be high (20,000 IU/kg BW) and should be repeated at least once daily for 3 days. If suppuration is already present, a longer course of antibiotics will be necessary, preferably for 7 to 10 days. Piglets treated early in the course of the disease will survive but may runt. Because of the common litter incidence in piglets and the occurrence of subclinical bacteremia, it is wise to also treat all littermates of affected piglets. Benzathine or benethamine penicillins can be used in conjunction with shorter-acting penicillins.

CONTROL

The principles of control of infectious diseases of the newborn are described elsewhere. Because the most frequent source of infection in foals is the genital tract of the dam, some attempt should be made to treat the mare and limit the contamination of the environment. Mixed bacterins have been widely used to establish immunity in mares and foals against this infection, but no proof has been presented that they are effective. On heavily infected premises the administration of long-acting penicillin at birth may be advisable. A major factor in the control of navel and joint ill in lambs is the use of clean fields or pens for lambing because umbilical infection originating from the environment seems to be more important than infection from the dam in this species. Docking should also be done in clean surroundings; if necessary, temporary yards should be erected. Instruments should be chemically sterilized between lambs. Regardless of species and where practicable, all parturition stalls and pens should be kept clean and disinfected, and the navels of all newborn animals should be disinfected at birth. Where screwworms are prevalent, the unhealed navels should be treated with a reliable repellent.

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Neonatal Neoplasia

Congenital neoplasia is rare, occurring at a substantially lower rate than in adults, and accounts for a minor percentage of findings in surveys of neonatal mortality. It is probable that genetic rather than environmental factors influence its development.

Clinical signs depend on the type of neoplasm and its site, and they can result in dystocia or abortion. A variety of tumors have been recorded in all large animal species and are predominantly of mesenchymal origin.

In calves, malignant lymphoma is most commonly reported. It is usually multicentric and also affects the skin. Sporadic bovine leukosis of young calves may also be present at birth. Other tumors reported predominant in calves include diffuse peritoneal mesothelioma, mixed mesodermal tumor, mast cell tumor, hemangiomas, and cutaneous melanoma.

Melanomas (both benign and malignant) also occur in foals and piglets. Duroc Jersey, Vietnamese pot-bellied pigs, and Sinclair miniature pigs have a high incidence of congenital malignant melanoma, which is fatal in approximately 15% of affected pigs but regresses spontaneously, and without recurrence, in the remainder.

A breed predisposition to cardiac rhabdomyoma is recorded in Red Wattle pigs.

Papillomatosis is rare, but **lingual papillomatosis** is reported as a cause of enzootic disease of piglets in China.