Canine neonatal mortality

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Abstract

Neonatal losses within the first few months of life are a common yet unavoidable problem in canine reproduction. It is important to understand the unique physiology of the canine neonate so that the main non-infectious and infectious causes of mortality can be anticipated and prevented. Birth weight is the single most important predictor of neonate survival. The neonate's body weight should be monitored twice daily for the first two weeks and any loss or failure to gain should be investigated. Clinical signs preceding neonatal mortality may include low or no weight gain, continuous vocalization, separation from the dam or other littermates, depression, abdominal distension, or loss of suckle reflex. There are numerous causes for neonatal mortality including peripartum hypoxia, growth retardation (intrauterine and postnatal), maternal aggression, neglect or rejection, nutritional deprivation resulting in hypoglycemia or dehydration, hypothermia, and pathogens (bacterial, viral and parasitic). Postmortem examinations provide essential information for causes of neonatal mortality and should be pursued aggressively to prevent further losses. Therapeutic goals of preventing neonatal mortality include supportive care and identification and eradication of the cause when known. In many cases, a number of simple actions can significantly reduce neonatal mortality.

Keywords: Canine, mortality, neonate, puppy

Introduction

Neonatal losses within the first few months of life are a common yet unavoidable problem in canine reproduction. The overall expected mortality rate in young dogs should be less than 12-15% of full-term births by the age of weaning. However, this could range from 5-35% depending upon factors that predispose to neonatal losses.[1-9] Of those deaths, approximately 50% are lost within the first seven days. Puppies are born much less mature than newborns of many other domestic species and thus are more dependent on care during the few weeks of life. It is important to understand the unique physiology of the canine neonate so that the main non-infectious and infectious causes of mortality can be anticipated and prevented. Fading puppy syndrome is a term that is used far too frequently to account of ignorance of normal neonatal needs and poor management[10-12]

The definition of a canine neonate is somewhat nebulous. Generally speaking, a neonate is less than six weeks of age (time of weaning) at which point the puppy would be referred to as pediatric. However, newborn puppies are less mature than newborns of other species. The most critical period in neonates is the first three weeks because this is when neurologic and behavioral maturation is completed. After three weeks, the eyelids and ear canals are open, thermoregulation is established and the puppy is capable of eating solid food. The following definitions have been suggested for neonatal puppies: perinatal period (less than one day), neonatal period (one to 21 days), maturation period (21-28 days) and preweaning period (28-42 days)[10,13]

Clinical examination of the canine neonate

Clinical signs preceding neonatal mortality may include low or no weight gain, continuous vocalization, separation from the dam or other littermates, depression, abdominal distension, or loss of suckle reflex.[6] The severity of clinical signs correlates negatively with survival, and death can occur within 18 to 24 hours from onset of clinical signs depending on the cause. A systematic physical examination should be performed on all neonates, especially if illness is suspected.

Daily weight gain is an excellent indicator of general health as healthy puppies gain weight continuously.[14] Neonates should be weighed at birth and then twice a day to accurately measure weight

gain.[15] Digital scales are more accurate and gram scales work better for small and toy canine breeds. It is normal for neonates to lose a little bit of weight (mostly water) in the first 24 hours. Neonates that lose more than 10% of the birth weight in the first day have a poor prognosis. After that, puppies should gain 5% to 15% of their birth weight daily, doubling their birth weight by ten days of age. This equates to one to three grams per day per pound of anticipated adult body weight.

As neurologic maturation is not complete until 21 days, accurate examination of the neurologic system requires understanding of when various reflexes (rooting, suckling, righting) develop and disappear. Presence of weakness in any of the reflexes indicates an ill neonate. The predominant posture is flexion for the first three to four days postnatally and then extensor tone will dominate,[6] The panniculus or cutaneous trunci reflex is present at birth. Flexor (pain or withdrawal) reflexes and a pain response to a noxious stimulus are present shortly after birth. A crossed extension reflex (pinching one foot and having the opposite limb extend) is present up to three weeks of age.[16]

In the normal neonatal puppy, the rooting and suckling reflexes disappear between 25 to 28 days.[6,17] However, these reflexes may persist longer in orphans.[10] The oral cavity should be free of congenital defects (e.g. cleft palate). The hydration status should be assessed by checking moisture of the mucous membranes because skin turgor of neonates is not as developed as in adults. If dehydrated, skin on the ventral abdomen and muzzle may appear a deeper red color. The skull should be examined for the presence of open fontanelles. A cranial nerve examination can be conducted in puppies after three weeks of age. Although the palpebral and corneal reflexes are present at birth, they are more easily visualized after the eyelids open.[18] Puppies' eyes open at nine to 16 days.[19] The menace response in puppies may not appear until after three weeks because the retina is not fully developed before this time. Visual depth perception develops by approximately 28 days.[20] Ear canals open in puppies between ten and 14 days of age, but sound orientation does not occur until approximately 21 days.[20]

Evaluation of mental attitude (e.g. depression, hyperexcitability with excessive vocalization) is also important. In the first two weeks, neonates spend most of their time nursing or sleeping.[20,21] They may crawl around on the lower part of their thorax for the first two weeks and after that time, they are able to lift their heads and maintain an upright position. Vocalizations occur as they seek food or are disturbed, but continuous crying is abnormal. It is abnormal for a healthy neonate to cry for longer than 20 minutes. Continuous crying usually indicates a cold or hungry puppy, but it may be a clinical sign of other painful or infectious processes.

On thoracic auscultation, the lungs should be clear and free of fluid. In a healthy puppy, breathing is regular and unlabored. The normal respiratory rate in neonatal puppies is 25 to 35 breaths per minute for the first two weeks of life, which decreases to normal adult rates between three to four weeks of age. The work of breathing in neonates is increased as a result of elevated airflow resistance due to the narrow diameter airways and the pliable chest wall (increased compliance). Neonates are more susceptible to respiratory fatigue and hypoventilation. For puppies that are delivered following cesarean, spontaneous breathing and vocalizing at birth are positively associated with survival at a week of age. Initial respiratory rate of newborn puppies is ten to 18 breaths per minute and they lack the typical pause between breaths that is normal in adult animals.[22] Heart rate is higher in neonates (>200 beats per minute) whereas blood pressure is lower (60±5 mmHg).[23,24] The neonatal heart rhythm should be a regular sinus rhythm that is not associated with breathing patterns because vagal reflexes do not develop until approximately eight weeks of age. Normal rectal temperature in the canine neonate is 35.0° to 37-2° C (95° to 99° F), which increases to 36.1° to 37.8° C (97° to 100° F) by 14 days. Poikilothermy gives way to autonomic thermoregulation by 28 days.[25]

The abdomen should be soft and not painful. Sick puppies lack normal bowel sounds on abdominal auscultation. The umbilicus should be dry and without any surrounding redness. Discoloration on the umbilicus or the ventral abdominal skin is indicative of sepsis and requires aggressive antimicrobial therapy. The presence and patency of the anus should be checked. The ability to urinate (by stimulating the area around the urethral opening) should be verified. Color of the urine

should be checked as a relative assessment of hydration status. Low specific gravity and glucosuria are common normal findings in neonates.[26] Orphans will need manual stimulation of the orifices with cotton or a soft cloth to elicit this reflex by owner the first two weeks until voluntary control of these functions is developed.[27] If the perineum is not stimulated, the bladder will continue to fill, causing abdominal distension. The anogenital reflex persists until three to five weeks of age, at which time postural control develops, which enables the puppy or kitten to assume a proper stance for urination.[28]

Neonates have decreased functional capacity of many organ systems because of incomplete development of these organs at birth. As they age, organ function increases. Hematology and serum biochemistry can be helpful to detect abnormalities of these organ systems as long as age appropriate reference ranges are used (Table 1). However, whenever possible, it is recommended to use the reference ranges established for each laboratory because of the lack of standardization among veterinary diagnostic laboratories. Neonates normally have mild serum phosphorus elevations as well as mild blood urea nitrogen, albumin, globulin, cholesterol, and hematocrit reductions. In addition, one- to three-day-old neonates have alkaline phosphatase concentrations that are 30 times higher than adult values due to colostral alkaline phosphatase.[29] Similar to alkaline phosphatase, gamma-glutamyltransferase concentrations are markedly increased in the first day after colostrum ingestion, with values being approximately 100 times higher than adult values.[29] These differences are short-lived, resolving within the first two weeks, but can be used as a surrogate marker of effective colostrum ingestion in puppies and kittens.[30]

Although an initial diagnostic database including a complete blood count and serum chemistry profile is desirable, obtaining a blood sample volume sufficient for running these tests may not be possible due to small body size of neonatal patients. The estimated blood volume of a canine neonate is 90 mL/kg of body weight,[19] such that not more than 10 mL/kg of body weight should be taken.[31] Small volume (0.6 mL) blood collection tubes are available from Becton, Dickinson and Company (Franklin Lakes, NJ; http://www.bd.com/vacutainer/pdfs/VS7629_ProductCat.pdf, BD Microtainer Blood Collection Tubes, BD Microtainer Plastic Clad Micro-Hematocrit Tubes). In most cases, a minimum database consisting of a hematocrit, total protein, glucose, and BUN is sufficient for making a diagnosis. An ear prick blood sample can yield a sufficient sample volume if only evaluating blood glucose concentrations.[19] Urine samples are generally easy to collect via perineal stimulation. In normal neonates, urine specific gravity is lower than adults, while urine protein and glucose may be higher.

Causes of canine neonatal mortality

There are numerous causes for neonatal mortality, most of which can be prevented. These have been divided into the following general categories: peripartum hypoxia; growth retardation (intrauterine and postnatal); maternal aggression, neglect or rejection; nutritional deprivation resulting in hypoglycemia or dehydration; hypothermia; and pathogens (bacterial, viral and parasitic). Of course, in many instances, overlap exists between these categories. Not all of the causes of canine neonatal mortality will be reviewed. For a more complete list of causes, as well as treatment regimens and prevention strategies, readers are referred to the text by Peterson M, Kutzler MA, editors: Small animal pediatrics—the first 12 months of life (St. Louis: Elsevier; 2011).

How the neonate is delivered into its postnatal existence is critical for its future survival. If the neonate is delivered naturally and if the mother does not remove the fetal membranes covering its mouth and nose, suffocation can occur. If the neonate is delivered by cesarean section, the amnion should be removed and a bulb syringe can be used to suction out the oronasal passages. Stronger methods of suction are not recommended due to potential injury to the airways and vagally-mediated bradycardia and laryngospasm.[32] Although historically a common method for removing amnionic fluid from the respiratory tract of neonatal dogs and cats, the swinging of newborns is no longer advocated because of potential cerebral hemorrhage from concussion.

Spontaneous breathing and vocalizing within one minute following delivery is highly correlated with neonatal survival. Neonatal resuscitation utilizes methods that assist with oxygen delivery to hypoxic tissues and prevent deterioration of acid-base stability by supporting ventilation and circulation and keeping the newborn warm.[22] Vigorous rubbing with gentle intermittent stretching stimulates breathing and clears airways of fluid. A tactile respiratory reflex can be stimulated in the genital and umbilical regions for the first three days of life.[33] In addition, in the mildly depressed neonate, vigorous tactile stimulation of the lumbar area by rubbing the fur backwards will help to elicit crying and further clear airways.[22] Sublingual injections of pharmacological respiratory stimulants (e.g. doxapram) are rarely used in resuscitation of human babies[34] and their use in veterinary medicine is controversial.[22] Their effectiveness is greatly decreased if the brain is hypoxic so administration during hypoventilation is unlikely to result in a favorable response.[31] The use of the Renzhong acupressure point (JenChung, GV26) stimulated with a 25-gauge needle to elicit spontaneous breathing has some effect.[35] The needle is inserted into the nasal philtrum at the base of the nostrils and rotated when bone is contacted (Figure1).

Figure 1. A line drawing depicting the Renzhong acupressure point (JenChung, GV26) to elicit breathing in apneic canine neonate. A 25-gauge needle would be inserted into the nasal philtrum at the base of the nostrils (arrow) and rotated when bone is contacted. Courtesy of Dr. Robin Waldvogel and the Chintimini Kennel Club.

If the neonate does not breathe despite these resuscitation efforts, an attempt to expand the lungs should be made. A tight-fitting mask can be applied to the face of the neonate and not more than 20 to 30 cm of water pressure can be applied for approximately three seconds until the chest wall expands.[22] The head should be extended to limit the amount of air forced into the stomach. Once the lungs have been expanded, artificial respiration can be continued at a rate of 30 breaths/minute, lasting approximately one second each, with no more than 10 cm of water pressure until the neonate is breathing spontaneously.[22] Ventilatory support is critical for the stressed neonate and high concentration oxygen is typically used. Temporary introduction of 30 to 40% oxygen environment may reduce distress if respiratory function continues to be inadequate. Because of the short-term nature of the oxygen therapy, the risk of oxygen toxicity is minimal.[22]

Following respiratory resuscitation (in puppies with persistently low heart rates), lateral chest compressions with the thumb and forefinger should be begun at a rate of one to two beats/second, pausing

for respiration.[22] In very barrel-chested breeds (i.e. Bulldogs), sternal compression may be more effective. The decreased heart rate in stressed puppies is likely due to myocardial hypoxia and is not vagally mediated.[36,37] There is little effect of atropine on heart rate in puppies before 14 days of age and because the low heart rate is most often due to myocardial hypoxia, myocardial damage could occur due to increased oxygen demand.[36,37] Therefore, the most important treatment for neonatal bradycardia is to increase respiration and attempt to correct the myocardial hypoxia.[33]

Neonatal survival at seven days of age following a cesarean section delivery is positively correlated when dams are anesthetized with propofol (4 to 6 mg/kg) and isoflurane as opposed to other general anesthetics.[38] Certain drugs, such as ketamine, thiopental, and xylazine, should be avoided.[38,39] A local block with lidocaine or bupivacaine will help reduce the level of isoflurane gas anesthesia.[38,39] Neonatal survival is higher following an elective cesarean section compared to an emergency cesarean section, with the overall 80% of neonates surviving to seven days of age. For elective cesarean section, a short-acting steroid such as prednisolone sodium succinate (Solu-delta-cortef®, Pfizer Animal Health, New York, NY) administered two to 12 hrs prior to surgery at a dose of 1.0 mg/kg has been shown beneficial in neonatal survival. Since neonates have relatively small airways, large tongues, and small nostrils, they are susceptible to hypoxia from the presence of fluid or mucus within the airways. In the normal birth event, spontaneous recovery of hypoxia and acid-base stability occurs over two to three hours.[40] Hypoxia in the newborn is usually due to an inability to completely inflate the lungs, which can be the result of inadequate lung surfactant production.[41] Before delivery, the presence of surfactant can be indirectly documented using the "foam stability test".[42] This technique was originally used in human obstetric medicine as a rapid test to determine the timing of a cesarean section. One milliliter of amniotic fluid is collected (via ultrasound-guided centesis or laparotomy) and is mixed with one mL of 100% ethanol in a glass tube. The solution is then vigorously shaken for 15 seconds. If surfactant is present, a ring of bubbles will form at the fluid-air interface and remain for at least 15 minutes (Figure 2). In human obstetrics, this method was used as a surgery room test to indicate fetal readiness for delivery. Results of this test in elective cesarean section delivery of canine fetuses have indicated that adequate surfactant production is not present until 62 days past the onset of the luteinizing hormone (LH) surge for female canine fetuses and 63 days past the onset of the LH surge for male canine fetuses. This sex difference is consistent with observations in human obstetrics, as female fetuses begin surfactant production earlier than males.[43]

Birth weight is an important survival determinant in most mammalian species. Low birth weight is associated with higher neonatal mortality because it is accompanied by immature physiological processes that can lead to extrauterine adaptive failure (e.g. inability to suckle and maintain blood glucose concentrations).[44] Normal birth weight in puppies is from 100 to 200 grams in small breeds, from 250 to 350 grams in medium breeds, from 400 to 500 grams in large breeds, to 700 to 900 grams in giant-breed dogs.[45] Newborns that are less than 25% of the average birth weight are at a higher risk of developing hypoglycemia, hypothermia, and pneumonia. Birth weight is not influenced by gender but is influenced by parental age and state of health, placental sufficiency, litter size, gestational nutrition, infections (bacterial, viral and parasitic), maternal environment (sanitation, stress) and congenital abnormality. Purebred puppies are more prone to congenital and hereditary defects that could result in neonatal mortality.[6] Inbreeding not only affects total puppy mortality, but also puppy mortality attributable to infection.[7]

Neonatal body weight should be monitored daily to ensure normal weight gain. Fading (or wasting) is characterized by a progressive clinical decline associated with anorexia, growth failure, depression, dehydration, and increasingly poor response to environmental stimuli.[10-12,44] Neonates that die within the first 48 hours have most likely succumbed because of starvation rather than infectious disease. Inadequate nutrition leads to dehydration and muscular weakness. Extrinsic problems that predispose

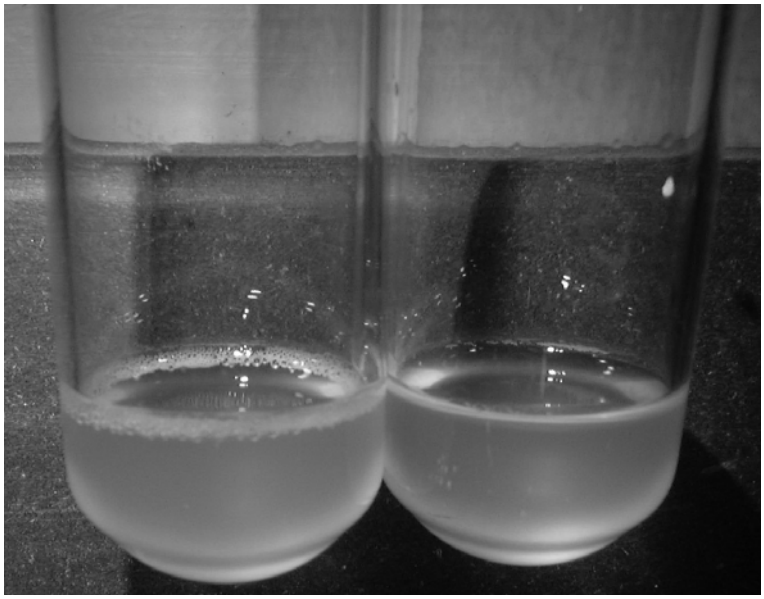

Figure 2. Before an elective cesarean section, the presence of surfactant can be indirectly determined using the "foam stability test." One mL of amniotic fluid is mixed with one mL of 100% ethanol in a glass tube and the solution is shaken vigorously for 15 seconds. If surfactant is present, a ring of bubbles will form at the fluid-air interface and remain for at least 15 minutes. (From Ruaux C: The respiratory system. In:Peterson M, Kutzler MA, editors: Small animal pediatrics: the first 12 months of life. St. Louis: Elsevier; 2011).

offspring to wasting include: inadequate lactation quality and quantity, excessive handling of the neonate, inexperienced or behaviorally maladjusted dam, inattentive caretakers, exposure to infectious agents.

Within the first 12 hours, neonates that have lost less than 10% of their birth weight or gained weight were at a lower risk for mortality.[46] Puppies should gain weight daily at a rate of two to seven grams per day for each kilogram of anticipated adult weight and they should double their birth weight by ten days of age. Puppies not gaining weight require supplementation. If one puppy is not gaining weight while the rest of the litter is, a physical examination should be performed. Providing the underfed puppy time alone with the mother may be beneficial. The rest of the litter may be pulled away from the dam for five to ten minutes, three or four times per day to give the underweight neonate an opportunity to increase milk intake. If the mother's milk is slow to come in, supplemental feedings are necessary for neonates that are not gaining weight or for orphaned puppies. A neonates's caloric requirement approximates 230 to 260 kcal/kg body weight daily (given over multiple feedings).[10,47] Most commercial milk replacers deliver approximately 1.0 kcal/mL.[10,47] The total daily feeding should be divided into at least eight feedings per day (approximately every two to three hours) during the first two weeks of life to reduce the risk of stomach overdistension, abdominal discomfort, diarrhea and aspiration. Smaller and toy breeds require more frequent feedings to prevent hypoglycemia. The frequency of feedings can slowly be decreased as the amount being fed increases.

Formulated puppy milk replacer is available commercially (i.e. Esbilac, Just Born, Renurse, Veta-Lac). Both powder and liquid forms are available. Powdered formula lasts longer, since the unused powder can be frozen for six months. Once powdered formula has been reconstituted, contents should be used within 48 hours, provided the unused portion is refrigerated in a glass container. Liquid milk replacer should be used within 48 hours once the can is opened, provided the unused portion is refrigerated. Ingredients and caloric density of the puppy milk replacer can vary with manufacturer. Puppies normally get their energy from fat during the first two weeks of life.[47] Milk replacer is made

from bovine milk and is lower in protein, calories, fat, calcium, phosphorus, and carbohydrates. Lactose concentrations are low in colostrum and lower in canine milk compared to bovine milk, which can cause diarrhea in puppies fed milk replacer.[47] It is advised to dilute milk replacer 25% to 50% with water or a balanced electrolyte solution for the first two days of feeding to minimize the occurrence of diarrhea. Because a neonate's stomach has a limited capacity, it is imperative that this ratio be correct to maintain proper hydration and meet the daily caloric requirement without overextending its fluid capacity. When choosing a milk replacer, it is important to review the product's energy content-to-fluid concentration ratio. Commercial milk replacer is superior to homemade versions because commercial products generally provide the correct balance of protein, fat, carbohydrates, vitamins, and minerals needed for growing neonates. If commercial milk replacer is temporarily unavailable, an emergency formula may be used. The emergency formula consists of one cup (250 mL) of whole cow's milk, three egg yolks, one Tbsp (15 mL) corn oil, 1 drop high-quality oral multiple vitamin solution and a small pinch of salt.[10] This formula is strictly for emergencies and should be replaced with a commercial milk formula as soon as possible. Puppies that are fed milk replacers should not be expected to maintain growth rates in parallel to those fed with dam's milk and will take longer to double their birth weight.[10]

Neonatal nutritional supplementation can be provided by either via bottle or tube feeding. When choosing a supplementation method, the strength of the neonate is the primary selection criterion. Bottle feeding might not be the best for weak neonates because their suckle reflex may be diminished and there is a possibility of aspiration into the lungs. In this case, tube feeding might be a better alternative. This process is not particularly difficult but needs to be done correctly. However, placement of orogastric tubes can be stressful to neonates, and if long-term feeding will be necessary, it may be more beneficial to place another type of feeding tube. Regardless of the supplementation method, prior to the feeding it is extremely important to make sure that the body temperature of the neonate is above 35.5º C (96° F). If the neonate's body temperature is too low, ileus develops and the ingested material will start to ferment instead of being digested, resulting in a bloated and distressed neonate.[10]

A red rubber catheter feeding tube should be measured and marked to help ensure that the tip of the tube is placed in the stomach. Depending on the size of the neonate, the clinician should use a 5-French (for puppies less than 200 grams), 8-French (for puppies 200 to 350 grams), 10-French (for puppies 350 to 500 grams) or 14-French (for puppies over 500 grams) [45]. Prior to placing the feeding tube, the distance from the tip of the nose to the last rib should be measured. Seventy-five percent of that distance should be marked on the tube with a permanent marker (Figure 3A). The feeding tube should extend into the puppy's stomach, but not far enough to cause kinking or looping and return to the esophagus. It is important to remeasure and re-mark weekly, as the patient grows.

Place the puppy in sternal recumbency with its head elevated and flexed (not extended). The puppy is not strongly or forcibly restrained. Excessive restraint can provoke struggling and increase risk for aspiration. Insert the tip of the tube along the left side of the roof of the mouth into the esophagus, following the path of least resistance (Figure 3B). No force is needed and most neonates will swallow the feeding tube easily. Advance to the mark that is measured on the tube. If the catheter is accidentally inserted into the trachea, the neonate might cough as a sign of the incorrect placement.[45] Another indication of incorrect catheter placement will be that the tube will not be able to be inserted fully to the premeasured mark. Correct placement of the feeding tube can also be ensured by the presence of negative pressure using the syringe on the end of the tube. Tube placement can also be checked by placing a stethoscope on the stomach, infusing a small amount of air into the tube, and listening for air in the stomach[45] If the tube is in the trachea, remove the tube and start over.

Once the tube is confirmed in the stomach, aspirate a small amount of gastric contents to check for any remaining formula and then attach a syringe containing the milk replacer. Administering the feeding is done with minimal restraint. Some puppies "prefer" to crawl around on a flat surface while being fed, with only sufficient restraint to keep the head elevated and maintain the tube placement.[45] If the stomach is empty, infuse the formula over a two-minute period to prevent overfeeding or feeding too

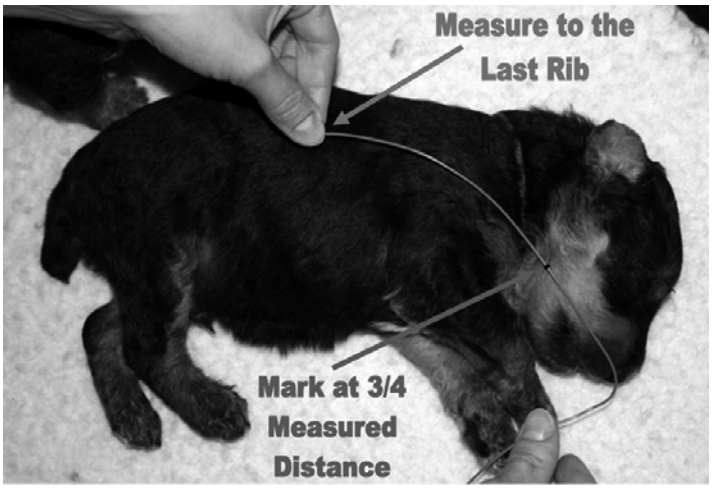

Figure 3. Passing an orogastric tube is not particularly difficult but needs to be done correctly. First, 75% of the distance from the tip of the nose to the last rib should be marked on the tube (A). The puppy is minimally restrained with the head elevated and flexed and the tube is passed along the left side of the roof of the mouth into the esophagus, following the path of least resistance (B). (From Rickard V: Birth and the first 24 hours. In Peterson M, Kutzler MA, editors: Small animal pediatrics: the first 12 months of life. St. Louis: Elsevier; 2011).

fast. The maximum stomach capacity for a puppy is approximately 40 mL/kg body weight (0.7 fluid oz (four teaspoons) per lb).[45] Many clinicians prefer to initiate supportive feeding with meals approximating 50% of calculated volumes, to avoid volume-related aspiration accidents, and to adjust gut flora to the regimen.[10] Monitor for gastric distention as over-distention can cause delayed gastric emptying, bloat, and diarrhea. Regurgitation can occur through the nose. Excess air intake while nursing can also cause bloat and make the puppy uncomfortable. After the feeding is complete, the catheter needs to be kinked before pulling it out to avoid milk dripping from the tip and being aspirated into the lungs. A new feeding tube should be used after eight to ten feedings as the tube will become less rigid and more likely to kink.[45] Feeding tubes should be disinfected and rinsed thoroughly between feedings in the same day.

Successful hand rearing of puppies can depend on several factors, including appropriate feeding schedule, selection of milk replacer, meeting caloric needs of the neonate, and proper feeding methods. Young dogs that are being tube fed should be monitored carefully for nasal discharge, regurgitation, bloating, abdominal discomfort, and diarrhea. These symptoms can indicate undesirable changes in gut flora or impeding medical complications (e.g. sepsis). Neonates being supplemented with milk replacers need to be monitored for constipation. Warm water enemas can be performed as needed if that condition occurs. After each meal, neonates need to be stimulated to urinate and defecate by rubbing the perineal and preputial areas with a cotton ball that has been soaked in warm water. Gastrointestinal motility is reduced in neonates less than 30 days old.[48] The formula should be warmed to body temperature to enhance gastrointestinal motility and prevent hypothermia. In addition, it is strongly advised to ensure proper body temperature, as hypothermia can also cause delayed gastric emptying.

Maternal aggression towards the neonates and cannibalization can be significant causes of neonatal mortality.[12] At times, calcium solutions (Cal-Pho-Sol®; 1 mL/10 lb SC; Neogen Corp., Lexington, KY) have been used to help with hypocalcemia-associated aggression. Care must be used with other preparations injected subcutaneously to avoid skin irritations. Light tranquilization with acepromazine (0.01 to 0.02 mg/kg) might be necessary initially until the problem resolves. Appeasing pheromone diffusers or collars may also be helpful in creating a calm, comfortable environment in the whelping room. In the cases of aggression, it might be necessary to place neonates in a small plastic box that has small round openings cut out for ventilation and longitudinal slits in the lid, so the mother can smell and hear her offspring, as well as see them move. Neonates are removed from the container for supervised nursing for the first 48 to 72 hrs until the new mothers are fully desensitized. In some cases of maternal neglect or rejection that do not include aggression, placing a few drops of oxytocin topically into the dam's nostrils will assist in mothering behavior. This author has had success with warming a placenta that was saved and frozen following delivery, rubbing the warmed placenta over the neglected or rejected neonates, and then allowing the dam to consume the remainder of the placenta and clean off the puppies.

Although not directly associated with maternal neglect, rejection and aggression, problems with the release of milk (galactostasis) or amount of milk present within the mammary gland (hypogalactia or agalactia) will result in neonatal mortality secondary to lack of adequate colostrum ingestion and starvation. Excessive noise and activity in the whelping room should be avoided to reduce maternal stress and allow for normal milk letdown. For galactostasis, the dam can be given low doses of oxytocin (0.2 to 2 U IM) 15 to 20 minutes before nursing in an attempt to induce milk release. Very attentive dams may be reluctant to leave their offspring to feed themselves, which results in decreased milk production. Food and water should be readily available to avoid this problem. For medical management of hypogalactia or agalactia, metoclopramide (0.1 to 0.2 mg/kg PO TID) or domperidone (2.2 mg/kg PO BID) have been used to help increase milk production. As a complementary treatment, acupuncture points LI4 and SI1 have also been used to promote lactation.

Water is the most common essential nutrient in which most animals are deficient. Neonates are especially susceptible to dehydration as a result of the physiologic immaturity of their kidneys. Although their bodies are more than 80% water, their ability to conserve water (concentrate urine) is significantly diminished since kidneys do not fully mature until six to eight weeks of age. Because of the immaturity

of the autonomic nervous system, canine neonates have an impaired ability to change systemic vascular resistance and cardiac contractility in response to dehydration. Water deficits are most frequently caused by prematurity; vomiting, diarrhea or pneumonia; excessive ambient temperature; and reduced intake secondary to inadequate suckling or poor lactation. The daily water requirement for neonates is 130 to 220 mL/kg of body weight per day.[47] Oral rehydration is preferred if gastrointestinal function is normal and the neonate is not hypothermic.[10] Since compromised neonates have increased susceptibility to bacterial infections, parenteral routes for rehydration need to be used with a scrupulously sterile technique. Subcutaneous or intraperitoneal administration are the routes used most frequently used to correct dehydration uncomplicated by hypoglycemia but are less desirable since absorption rates are slower and less predictable. Intravenous (external jugular) or intraosseous (IO; femur or humerus) administration is more difficult and stress producing,[10] but necessary if dehydration is concurrent with hypoglycemia, which is often the case. Dehydration should be corrected with balanced crystalloid fluids (lactated Ringer's solution or Normosol-R® with 5% dextrose; Hospira, Inc., Lake Forrest, IL). In all cases, administration of warmed fluids is necessary. Fluid deficits should be incrementally corrected over 12 to 24 hours. An initial rate of 30 mL/kg of body weight should be used to correct dehydration and then adjusted as needed based on response.[31] A maintenance fluid dose in neonates is three to six mL/kg of body weight/hour.[22] Serial weight assessments are the most accurate method for assessing hydration in neonates and for continued monitoring for reoccurrence. Careful monitoring is essential because fluid overload is possible due to the diminished kidney function. It is best to use a microdrip administration set or a syringe pump to avoid fluid overload.[31]

Many neonatal deaths result from inadequate nutritional intake or the inability of the neonate to adequately digest and absorb nutrients as a result of their immature digestive system. A healthy mother who is well-nourished should be able to provide complete nutrition for her puppies for their first four weeks. A healthy puppy will nurse vigorously several times a day and gain weight on a daily basis. If insufficient milk is available for consumption or if neonates are unable to nurse, hypoglycemia will result in neonatal mortality within 48 hours. Glucose in the blood is closely regulated and normally maintained by three major mechanisms: intestinal absorption, hepatic production, and, to a lesser degree, renal production. Glucose levels are lowest immediately after birth and then significantly increase after approximately three days with normal suckling. At birth, the gastrointestinal tract must transition from processing amniotic fluid to digesting milk. The release of hormones and digestive enzymes and the activation of secretion, motility, and absorption are adaptations that begin shortly after birth. These changes are critical to allow the gastrointestinal tract to perform required functions. The intestinal mass of puppies increases in the first 24 hours. Intestinal growth is decreased if milk replacer is fed in place of colostrum, possibly caused by missing hormones, fat, or other colostral components. Neonates have decreased pancreatic digestive enzymes, which permits intestinal absorption of immunoglobulins from the colostrum. Pancreatic lipase production increases over the first three weeks as the amount of milk fat increases, and pancreatic amylase production does not begin until after 21 days of age. However, canine milk contains the digestive enzyme amylase, which helps digest milk sugars in the neonatal gastrointestinal tract. Neonatal hepatic glycogen storage is minimal and dependent upon maternal nutrition during pregnancy. Hepatic glycogen reserves are depleted within 24 hours during fasting, resulting in hypoglycemia (serum glucose <40 mg/dl).[31] Maintaining normoglycemia is important for the neonates' neurologic status because they have a brain-to-body mass carbohydrate requirement two to four times greater than adults. In addition to having reduced potential for glycogenolysis, they have minimal capacity for glucose derivation from gluconeogenic branched chain amino acids. In comparison with adults, neonatal dogs have poor glycemic regulation that is attributed to a relative insensitivity to endogenous insulin and suboptimal counter-regulatory hormone responses (cortisol and epinephrine). Postweaning transient juvenile hypoglycemia is of particular concern in miniature and toy breeds of dogs as a result of poor glycemic regulation. Puppies with infectious disease (sepsis) or a portosystemic shunt will also develop hypoglycemia from increased glucose utilization. In addition, disease states such as

diarrhea, dehydration, or hypothermia may exacerbate hypoglycemia. To prevent hypoglycemia, neonates should not be fasted prior to anesthesia.

Glucose supplementation is essential for sick neonates, and the treatment is aimed at achieving a normoglycemic state. Lactate-containing fluids are preferred when treating symptomatic hypoglycemic puppies because lactate precedes use of alanine or glutamine for gluconeogenesis in puppies and because lactate is preferentially used in the brain. Any fluids that are administrated should be warmed to 37° C (100º F) to prevent hypothermia. In the event of a hypoglycemic crisis, neonates should be treated with ten to 25% dextrose at one to two mL/kg of bodyweight IV.[31] Neonates have an immature metabolic regulatory mechanism, therefore, hyperglycemia needs to be watched for, and dextrose administration needs to be adjusted accordingly. Dextrose should not be administered subcutaneously at these concentrations because of the potential of skin sloughing. If the neonate is not too weak, has a good circulation, and is attempting to nurse, then a 50% dextrose solution can be applied to the gums. However, oral dextrose or corn syrup rarely reverses a hypoglycemic crisis. L-carnitine (50 mg/kg PO BID) increases the liver's ability to convert fat to glucose, and it can be given to prevent hypoglycemic episodes from recurring.

Thermoregulation is another challenge that is exacerbated in immature dogs. Puppies have a larger surface area-to-body weight ratio, with high radiation and evaporative heat losses, an inability to shiver and vasoconstrict in response to decreasing temperatures, a small amount of subcutaneous fat and high water composition, and an immature thermoregulatory system.[49] Hypothermia can decrease neonatal responsiveness to attempts at resuscitation, as it leads to bradycardia (40 to 50 beats/minute), tissue hypoxia, and metabolic acidosis.[50] After the puppy is born, its body temperature will gradually decrease from the dam's body temperature to that of a neonate over the first 30 minutes of life.[50] Normal body temperature of newborn puppies ranges from 35.0° to 37.2° C (95° to 99° F).[10,50] Temperature guidelines for the prevention of hypothermia in puppies are 29° to 32° C (85° to 90° F) for the first week of age, 27° C (80° F) for the second and third weeks and 21° to 24° C (70° to 75° F) for the fourth and fifth weeks and 21° C (70° F) thereafter.[49,51] Ambient temperature should be monitored via thermometer and drafts must be prevented. Excessive ambient heat is recognized by changes in litter positioning (separated vs normal huddling), character of respiration (hyperthermia results in hyperventilation and open-mouthed breathing), elevated rectal and skin temperature, and distress vocalizations that express discomfort.[10] External heat sources most commonly used are heat lamps, heating pads, and warm water bottles. The latter two need to be used with caution since weak neonates might not be able to crawl away from the heat source, resulting in burns and thermal injury. Another important factor is humidity, which should be maintained at 50 to 55% to avoid excessive drying of the skin and dehydration. However, humidity in excess of 60% can result in hyperthermia and other complications.

Hypothermia suppresses appetite (resulting in failure to suckle), possibly as an adaptive response to reduce risk for aspiration. Hypothermia also causes intestinal ileus at temperatures below 34.4° C (94° F).[10] Decreased intestinal motility can cause fermentation of milk in the stomach, resulting in bloat and severe abdominal pain. Subsequently, there is increased pressure on the diaphragm, which causes labored breathing and dyspnea. These factors in turn cause the neonate to swallow more air and thus worsen the bloating. Severe bloating can result in circulatory collapse and death. If hypothermic neonates are tube fed, the milk replacer is usually regurgitated and aspirated.

Hypothermic neonates should be slowly warmed over 30 minutes to two hours and not faster than 1º C (2° F) per hour.[10] Rapid warming increases metabolic demand, with risk of exceeding the delivery capacity of circulatory and pulmonary function; this can cause loss of cardiovascular integrity, secondary hypoxia, cerebral changes, and sepsis. If the body temperature is raised more than 2° C (4° F) per hour, life-threatening organ failure (specifically the heart and kidneys) can result. Neonates should be rotated often to ensure even warming, and rectal temperatures should be checked frequently. Warm IV or IO fluids can also be given to raise the body temperatures, but the temperature of the fluids should not be

more than two degrees higher than that of the body. Slow warming followed gastrointestinal parenteral fluid support are the primary therapeutic steps. Oral alimentation should not be re-established until normothermia is achieved.[44] Neonates that have been given supportive warming should be monitored frequently recurrence of hypothermia.

To prevent hypothermia, environmental temperatures need to be increased because higher temperatures will help neonates maintain their core temperature. If neonatal anesthesia or surgery is necessary, appropriate steps should be taken to prevent hypothermia by limiting heat loss, such as clipping only a minimal amount of hair and avoiding alcohol-containing antiseptics. Side effects associated with hypothermia include cardiovascular alterations (bradycardia, hypotension, decreased cardiac output, arrhythmias), prolonged recovery times and drug metabolism, as well as increased infection rate and decreased wound healing.[15]

Infectious diseases are the second most important cause of mortality and account for a large proportion of newborn losses.[4] However, infectious causes of neonatal mortality are generally secondary to management problems. Predisposition to infection depends on: stress, environment, exposure to pathogens, and decrease in systemic immunity due to inadequate colostrum ingestion. Colostrum deprivation following birth hypoxia greatly increases risk for septicemia, especially in low birth weight puppies.[52] Puppies that do not ingest adequate colostrum are more susceptible to infection until about 35 days of age. In puppies, negligible amounts (<5%) of maternally derived IgG are transferred transplacentally.[53,54] The remainder of IgG is transferred in the colostrum, resulting in an initial spike in globulins immediately after colostral ingestion. Canine colostrum has fifty times the concentration of antibodies than canine milk (500 to 2200 mg/dL compared to 10 to 30 mg/dL, respectively). An adequate ingestion of colostrum must occur within the first 24 hours to acquire passive immunity from the mother. Gut permeability to immunoglobulins starts to decline eight hours after birth, and no further absorption is possible after 48 to 72 hours.[55] The half-life of IgG in puppies is ten days.

Failure of passive transfer is typically diagnosed by measuring IgG in serum via radial immunodiffusion (RID) method. However, this test is not readily available and the results can be difficult to interpret. Adequate colostrum ingestion can be indirectly assessed in neonatal puppies by measuring serum alkaline phosphatase and/or gamma glutamyl transferase as both of these enzymes are found in colostrum at concentrations 30 times and 100 times adult serum concentrations, respectively.[30] For neonates that have not received adequate colostrum, maternal serum can be administered orally to a neonate less than 12 hours old via a feeding tube in the amount of 150 mL/kg of body weight (divided into multiple feedings). If neonates did not receive any colostrum within the first 24 hours, serum can be administered at a dose of 50 mL/kg of body weight SC, three times at six to eight hour intervals. Hyperimmune canine serum preparations can be purchased (www.hemopet.org) and may be particularly useful for the treatment of herpes virus infections (see below).

Hypoxia predisposes neonates to fatal infectious disease. Hypoxia can result from respiratory distress syndrome after compression of umbilical circulation,[40] obstetric procedures,[38] or hypoxic damage,[56] hypothermia,[57] hypoglycemia,[58] dehydration and congenital abnormalities.[14] Neonatal sepsis occurs in puppies secondary to hypoxia-induced bacterial translocation from the intestinal tract into the bloodstream, resulting in a fatal necrotizing enterocolitis, even in the absence of mucosal lesions.[56] However, colostrum-fed puppies did not develop enterocolitis, illustrating the importance of adequate colostrum ingestion.[59] Bradycardia and hypotension frequently accompany hypoxia.[10]

Infection with bacteria, rather than viruses, is the most common cause of infectious mortality at this young age.[4] The most common route of entry for bacterial organisms is through the umbilicus. However, bacteria can also be introduced orally. Neonates are born with a sterile gastrointestinal system and develop their own intestinal flora over the first few days. The neonate's digestive system is very fragile and is easily affected by its diet, the environment, or pathogens because the physical defense against infection is reduced in the newborn. Since the production of gastric hydrochloric acid has not yet fully developed, stomach acidity is lower in neonates than in adults.[60] As a result of this decrease in the

acid barrier, the defense against infectious agents is decreased, allowing greater survival of bacteria and increased susceptibility to gastrointestinal infections. The most common manifestation of gastrointestinal upset is diarrhea.

The most commonly reported bacterial causes of neonatal sepsis include: *Escherichia coli*, and other gram-negative enteric organisms (e.g., *Enterobacter* sp.), *Campylobacter* sp., *Clostricium. perfringens* type A, α-hemolytic *Streptococcus* sp. (e.g., *S. canis*), *Staphylococcus* sp. *(S.aureus, S.intermedius)*, and *Salmonella*.[3,4,61-66] Unfortunately, post-mortem cultures are how most neonatal bacterial infections are diagnosed.

Aspiration of meconium, milk or other substances can result in pneumonia and systemic bacterial infection. Aspiration pneumonia may occur following bottle-feeding or with misplacement of a gastric feeding tube. Around the time of weaning and the transition to solid food, aspiration pneumonia can also occur secondary to esophageal or pharyngeal dysfunction, congenital megaesophagus, persistent right aortic arch, or cricopharyngeal achalasia. The clinical signs of aspiration pneumonia are essentially the same as infectious pneumonia (e.g., increased respiratory rate, fever, and a productive cough). Respiratory sounds may be harsh. Crackles may be auscultated over the affected regions of the thorax. Wheezing is less common but may be heard if there is significant bronchial involvement. Radiographic signs of aspiration pneumonia are variable and may not be present until 12 to 24 hours after aspiration. Bacterial pneumonia typically shows a cranioventral distribution of interstitial to alveolar patterns, viral pneumonias tend to show a more diffuse, interstitial pattern. Right cranial and medial lung lobes are most commonly affected in animals who aspirate while in sternal recumbency. Other lobes may be affected depending on positioning at the time of aspiration. A high percentage of neonatal puppy mortalities have combinations of pulmonary congestion, edema, hemorrhage, and atalectasis.[10]

Treating pneumonia in a neonatal dog is often unrewarding so efforts should be concentrated on prevention. Neonates with pneumonia usually require intensive monitoring in a 24-hour care facility. Oxygen supplementation via nasal oxygen cannula or use of a humidified oxygen environment cage is needed to prevent hypoxia and bradycardia. Ventilation is improved when inflammatory mucus and exudates are cleared from the airways. Maintaining airway hydration by saline nebulization and mucolytic agents (e.g., *N*-acetylcysteine) will help clear exudates from the respiratory tract. Cough suppressants are contraindicated.

Antibacterial therapy is critical in the management of bacterial pneumonia. Relatively long-term antibiotic therapy is required for either four weeks or until ten days after radiographic resolution. Ideally antibiotic selection is based on the results of culture and sensitivity from lower airway fluids or lung aspirates. However, the collection of these samples may represent a severe anesthetic risk in compromised neonatal patients. Awaiting results of these cultures may also unduly delay therapy in critical patients. Subsequently, empirical selection of an antibiotic that is safe in neonates is generally used.[67] When selecting an antibiotic that is safe in neonates, drugs that require major hepatic metabolism should be avoided.[68,69] Highly protein-bound drugs will exert a greater clinical effect on neonates compared to adults as a result of the higher quantities of unbound or active drug in the plasma due to the lower plasma albumin concentration of neonates. Renal clearance is decreased until the puppy nears six weeks of age.[68,69] Since elimination is decreased, the half-life of drugs is longer and the interval between doses should be increased. Compared to adults, neonates have increased percentage of total body water and decreased percentage of body fat. As a result, the volume of distribution for the water-soluble drugs is increased, so the dose of water-soluble drugs used in neonates should also be increased. In contrast, the volume of distribution for the lipid soluble drugs is decreased. In this case, the dose of lipid soluble drugs in neonates should be decreased.[31]

Treatment with antibiotics prior to sensitivity results could be life-saving. Thus empirical use of safe, broad-spectrum bactericidal antibiotics is usually recommended. Safe antibiotics in the neonate include cephalosporins, penicillins, clavulanic acid, macrolides, trimethoprim-sulfonamide, and amikacin (if properly hydrated).[49] Ceftiofur, a third-generation cephalosporin, administered at a dose of 2.5 mg/kg

BID SC for five days, is one of the better choices because it has minimal effects on the normal neonatal gastrointestinal flora. Combinations of amoxicillin with clavulanic acid or trimethoprim with sulfonamide are also reasonable first-line choices for antibiotic therapy. Fluoroquinolones should be avoided because of the potential for cartilage damage in growing animals.

Common viral causes of neonatal mortality include canine herpesvirus, canine minute virus (parvovirus type I), canine parvovirus type II (CPV-2), canine distemper virus. Puppies infected with canine distemper virus transplacentally can develop neurologic signs within six weeks of birth.[70] Canine parvovirus type 1, the causative agent of minute virus of canines, also causes birth of weak puppies.[71] Neonatal infections with canine herpes virus can be acquired in utero, by contact with infectious vaginal fluids during passage through the birth canal, by exposure to infected littermates, from oronasal secretions of the dam, or by fomite transmission. Herpes virus is not stable in the environment and must be acquired from a persistently infected carrier. Infection with canine herpesvirus causes an acute, rapidly fatal illness associated with hepatic necrosis. Puppies may have predisposition as a result of their poor thermoregulation and inability to mount a febrile response. Generalized, fatal infections develop in puppies exposed when less than three weeks of age. Puppies exposed when older than three weeks are comparatively resistant and often develop mild or inapparent infection and passage of maternal protective antibodies or lymphocytes in colostrum can prevent illness in neonates. Clinical signs of herpesvirus infection in puppies under three weeks of age include lethargy, decreased suckling, persistent crying, yellow-green diarrhea, rhinitis, abdominal pain, and incoordination. A distinct feature is the absence of fever. Thrombocytopenia, evident by petechial hemorrhages, develops associated with disseminated intravascular coagulation as a result of the vasculitis. Diffuse necrotizing vasculitis and spread of virus into parenchymal organs, including the adrenal glands, kidneys, lungs, spleen, and liver, result in multifocal organ necrosis. Meningoencephalitis is common, although puppies infected at less than one week of age usually die before neurologic signs develop. Survivors that had neurologic signs may have permanent neurologic deficits, most commonly cerebellar vestibular deficiencies. Ocular involvement may cause panuveitis, cataracts, keratitis, retinitis, and subsequent blindness. Death frequently occurs within 24 to 48 hours after onset of clinical signs. Definitive diagnosis is made based on history, clinical signs, pathologic changes, and virus isolation. Gross pathologic findings include disseminated multifocal 1- to 2-mm hemorrhages and areas of necrosis that are distinctly circumscribed in the liver, kidney, and lungs. Herpes viral replication might be inhibited by maintaining body temperature above 38º C (101° F). Acyclovir suspension can be attempted at a dose of 20 mg/kg PO every six hours for seven days. Impeccable hygiene (from whelping through weaning) and strict biosecurity measures can reduce the incidence of canine herpesvirus mortalities. In countries where available, prophylactic canine herpesvirus vaccination at the time of breeding and at pregnancy diagnosis is a successful way to prevent disease outbreaks and neonatal losses.

Common parasitic causes of neonatal mortality include *Strongyloides stercoralis*, *Neospora caninum* and *Toxoplasma gondii*. *Strongyloides stercoralis* is a zoonotic parasite that is transmitted from dam to pups via milk.[72] Overcrowding and poor hygiene in a kennel are predisposing factors.[73,74] Young animals with heavy burdens have diarrhea and weakness, which progresses to emaciation and death, sometimes secondary to *C. perfringens* overgrowth.[65] Fenbendazole is the drug of choice in treatment of *S. stercoralis* infection.[72] Prenatal or lactationally acquired protozoal infections with *Neospora* and *Toxoplasma* can result in acute severe neonatal illness and death.[75,76] Systemically infected puppies can appear normal at birth and continue to nurse but insidiously become lethargic, inappetent, and dyspneic and may demonstrate mucopurulent oculonasal discharge and develop progressive neurologic abnormalities with illness, culminating in death.[76] Dissemination to multiple organs usually involves the liver and leads to jaundice, hepatomegaly, and abdominal effusion.[76] Multifocal necrotizing hepatitis or cholangiohepatitis causes anterior abdominal pain and peritoneal effusion and usually is associated with vomiting, diarrhea and jaundice. Diagnosis is definitively confirmed by finding tachyzoites in histologic or cytologic specimens.[76] Clindamycin is the drug of choice for treating clinical toxoplasmosis in dogs

and also is recommended for pregnant animals.[77] Oral and parenteral dosing is similar, 10 to 20 mg/kg body weight BID PO or IM for four weeks. Clinical response is usually evident as early as 48 hours.

Postmortem examinations provide essential information for causes of neonatal mortality and should be pursued aggressively to prevent further losses. If possible, the entire remains should be shipped via next-day delivery to a veterinary diagnostic laboratory for examination. Cases from which only tissue samples were sent were significantly less likely to lead to a conclusive diagnosis. The body should be kept in the refrigerator (not frozen) until shipping and shipped with ice packs.

Conclusion

In conclusion, more neonates die from improper husbandry and inadequate nutrition than infectious disease. Hypoglycemia, dehydration, hypoxemia and hypothermia are the main mechanisms for neonatal losses. Birth weight is the single most important predictor of neonate survival. The neonate's body weight should be monitored twice daily for the first two weeks and any loss or failure to gain should be investigated. Therapeutic goals of preventing neonatal mortality include supportive care and identification and eradication of the cause when known. In many cases, a number of simple actions can significantly reduce neonatal mortality.

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Table 1. Normal hematology and serum biochemistry reference ranges for canine neonates from birth to 8 weeks of age.

	Birth	Week 1	Week 4	Week 8
RBC ($\times 10^6/\mu l$)	4.7-5.6	3.6-5.9	3.6-4.9	4.5-5.9
Hemoglobin (g/dl)	14.0-17.0	10.4-17.5	8.5-10.3	10.3-12.5
PCV (%)	45.0-52.5	33.0-52.0	27.0-33.5	31.0-39.0
nRBC/100 WBC	0-13	0-11	0-4	0-1
Reticulocytes (%)	4.5-9.2	3.8-15.2	4.6-6.6	1.0-6.0
Total WBC ($\times 10^3/\mu l$)	6.8-18.4	9.0-23.0	8.5-16.4	12.7-17.3
Segmented neutrophils	4.4-15.8	3.8-15.2	3.7-12.8	6.2-11.8
Band neutrophils	0-1.5	0-4.8	0-0.3	0-0.3
Lymphocytes	0.5-4.2	1.3-9.4	1.0-8.4	3.1-6.9
Monocytes	0.2-2.2	0.3-2.5	0.3-1.5	0.4-1.7
Eosinophils	0-1.3	0.2-2.8	0-0.7	0-1.2
Platelets ($\times 10^3/\mu l$)	178-465	282-560	130-360	240-435
Albumin (g/dl)	1.76-2.75	1.71-2.5	2.17-2.97	2.38-3.22
ALP (U/L)	452-6358	195-768	153-490	153-527
ALT (U/L)	9.1-42.2	4.1-21.4	4.3-17.4	10.3-24.3
Bilirubin (mg/dl)	0.04-0.38	0.01-0.18	0.02-0.15	0.01-0.11
BUN (mg/dl)	29.5-118	29.1-66.7	13.1-46.2	16.8-61.4
Calcium (mg/dl)	10.4-13.6	11.2-13.2	10.4-13.2	10.8-12.8
Cholesterol (mg/dl)	90-234	158-340	177-392	149-347
Creatinine (mg/dl)	0.37-1.06	0.28-0.42	0.25-0.83	0.26-0.66
GGT (U/L)	163-3558	—	—	—
LDH (U/L)	1.8-17.0	0.2-17.7	1.2-9.0	1.6-7.3
Glucose (mg/dl)	76-155	101-161	121-158	122-159
TP (g/dl)	3.7-5.77	3.26-4.37	3.71-4.81	4.04-5.33
Triglycerides (mg/dl)	45-248	52-220	36-149	39-120
Phosphorus (mg/dl)	5.26-10.83	8.35-11.14	8.66-11.45	8.35-11.14

RBC, Red blood cells; *PCV*, packed cell volume; *nRBC/100 WBC*, number of nucleated red blood cells per 100 white blood cells; *total WBC*, total white blood cell count; *ALP*, alkaline phosphatase; *ALT*, alanine transferase; *BUN*, blood urea nitrogen, *GGT*, gamma-glutamyltransferase, *LDH*, lactate dehydrogenase; *TP*, total protein.

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