

## **PEDIATRIC CRITICAL CARE**

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The unique physiological systems of pediatric and neonatal patients make diagnosing and treating diseases and conditions challenging. Hemodynamic parameters, drug dosages, laboratory data, and diagnostic imaging differ significantly compared to adults of the same species. This presentation will cover the normal values as well as the abnormal findings and treatment of several common conditions affecting neonatal and pediatric dogs and cats. New discoveries on microalbuminuria and coagulation alterations will be discussed.

### **Hypovolemia**

#### *Clinical Signs Absent*

Hypovolemia results in decreased perfusion and subsequent decreases in oxygen delivery to tissues and most commonly occurs in neonates due to diarrhea, vomiting, or decreased intake. In adults hypovolemia is compensated for by increasing the heart rate (HR), concentrating the urine, and decreasing urine output. In neonates compensatory mechanisms may not be adequate or even existent. Contractile elements make up a smaller portion of the fetal myocardium (30%) compared to the adult myocardium (60%) making it difficult for the fetus to increase its contractility in response to hypovolemia. Neonates also have immaturity of the sympathetic nerve fibers in the myocardium and cannot maximally increase HR in response to hypovolemia. Complete maturation of the autonomic nervous system does not occur until 8 weeks in puppies.

#### *Blood Pressure is Low*

MAP was 49mmHg in normal puppies at 2 months of age compared with a MAP of 94mmHg at 9 months of age. The muscular component of the arterial wall appears to be immature at birth and is thought to be the cause of the relatively low BP. In adults renal auto-regulation of BP occurs over a wide range of systemic arterial pressures. Neonatal kidneys cannot do this and the GFR decreases as the systemic BP decreases, making restoration of fluid volume critical in neonates.

#### *Azotemia Does Not Occur*

Immature kidneys prevent concentration and dilution of urine in response to hypovolemia which doesn't normalize until ~10 weeks. The capacity to concentrate urine increases almost linearly with age during the first year in humans. Inefficient countercurrent mechanisms, decreased sodium resorption in the thick ascending loop, relatively short loops of Henle, and decreased urea concentration are thought to be causative. Simultaneously, BUN and creatinine are lower in neonates than adults, making monitoring of azotemia very challenging in neonates. Skin has increased fat and decreased water content compared to adults and skin turgor cannot be used to assess dehydration. Mucous membranes remain moist in the face of severe dehydration in neonates and cannot be used to adequately assess it.

#### *Fluid Requirements are Higher*

Due to neonatal fluid requirements (higher), and increased losses (decreased renal concentrating ability, higher respiratory rate, and higher metabolic rate); dehydration can rapidly progress to hypovolemia and shock if not adequately treated. The most common causes of hypovolemia in neonates are gastrointestinal disturbances (e.g., vomiting, anorexia, and diarrhea) and inadequate feeding. The most common cause of diarrhea in neonatal puppies and kittens is owner overfeeding with formula.

#### *Difficulties in Assessment*

Due to the difficulties in adequately assessing hypovolemia in neonates, there are some assumptions that should be made. All neonates with severe diarrhea, inadequate intake, or severe vomiting should be assumed to be dehydrated and hypovolemic and treatment should be initiated immediately. Treatment includes fluid therapy, monitoring of electrolyte and glucose status, and nutritional support. We suggest weighing the patient at least q12h, preferably q8h on the same, accurate gram scale. Dehydration is likely when the urine specific gravity reaches 10.20 and this should be monitored as an indicator of

rehydration. We start with a bolus of 45ml/kg of warm isotonic fluids in severely dehydrated or hypovolemic animals. This is followed by a constant rate infusion of maintenance fluids (80ml/kg/day) together with losses. Losses can be estimated (i.e., two tablespoons of diarrhea is equal to 30 ml of fluid). If the neonate is hypoglycemic or not able to eat, dextrose is added to the IV fluids at the lowest amount that will maintain normoglycemia (i.e., start with 1.25% dextrose).

### **Hypoglycemia**

#### *Glucose Metabolism Issues*

A combination of immature glucose feedback mechanisms, inefficient hepatic gluconeogenesis, decreased liver glycogen stores and loss of glucose in the urine make hypoglycemia a real concern in this population. Urinary glucose reabsorption does not normalize until ~ 3 weeks in puppies. The brain requires glucose for energy in the neonate and brain damage can occur with prolonged hypoglycemia. The fetal and neonatal myocardium use carbohydrate (glucose) for energy rather than the long chain fatty acids used by adult myocardium. In summary, the neonate has an increased demand, increased loss, and a decreased ability to synthesize glucose compared to adults.

#### *Clinical Signs Absent*

Clinical signs of hypoglycemia can be hard to recognize due to inefficient counter-regulatory hormone (epinephrine) release in hypoglycemia in neonates. In adults, the counter regulatory hormones are released (i.e., cortisol, growth hormone, glucagon, and epinephrine) in response to low blood glucose and facilitate euglycemia by increasing gluconeogenesis and antagonizing insulin. Clinical signs of hypoglycemia, if seen, may include lethargy and anorexia. Vomiting, diarrhea, infection, and decreased intake all contribute to hypoglycemia in neonates. Infusions of 1ml/kg of 12.5% dextrose (i.e., dilute 50% dextrose 1:4) followed by a CRI of isotonic fluids supplemented with 1.25 to 5.0% dextrose are required to treat this condition. It is important to follow any bolus of dextrose with a dextrose CRI to prevent rebound hypoglycemia.

### **Sepsis**

#### *Difficult to Detect*

Sepsis is common in pre-term neonates and is a major source of morbidity and mortality in humans. Clinical signs, as in hypovolemia, are often subtle and sepsis can be difficult to detect in this population. The human pediatric definition of sepsis is SIRS plus a proven infection. SIRS criteria use 2 of the following; an abnormal WBC count, body temperature, HR, or RR. All of these criteria are significantly different and variable compared with adults. A study looking at 30,000 absolute neutrophil counts in healthy neonates reported ranges from 1,500/ul to 41,000/ul. Another study reported results in over 200,000 infants and concluded that no CBC variable was helpful in identifying sepsis. Since neonatal hypothermia is common alterations in body temperature are often an indicator of the environmental heat either overzealous or not delivered. Among 395 symptomatic infants with blood culture positive sepsis only 10.8% had alterations in body temperature. In a study in newborns with positive documentation of infection at autopsy only 14% had pre-mortem positive blood cultures.

#### *New Assay*

Recently, Anil, et al. reported on the predictive value of microalbuminuria for sepsis in neonates. SIRS is associated with endothelial damage and increased capillary permeability with transient albuminuria occurring during glomerular inflammation. The degree of albuminuria can be assessed by a spot urine albumin-creatinine ratio (ACR). Increased ACR has been suggested as an early marker of SIRS and an increased ACR has been observed during sepsis, pancreatitis, trauma, and surgery in humans. ACR at admission and 24 hours after admission in critically ill children predicted mortality and correlated with severity scores. In neonates ACR was elevated with SIRS compared to those without SIRS and there were parallel increases in ACR, inotropes used, organ failure and mortality. ACR is a simple, inexpensive biomarker that may identify neonates that are septic. A drawback is the lack of normal values in neonatal puppies and kittens.

#### *Causes of Sepsis*

In veterinary medicine neonatal sepsis is most often secondary to wounds (tail docking, umbilical cord ligation) or respiratory & gastrointestinal infections. Clinical signs that may be associated with sepsis include crying, reluctance to nurse, decreased urine output, and cold extremities.

#### *Treatment of Sepsis*

Aggressive fluid resuscitation is associated with decreased mortality in children with sepsis and in several animal models. Large volumes of fluid are often needed in septic patients due to increased capillary permeability (increased losses) and vasodilation. We start with a bolus of 45ml/kg of warm isotonic fluids and monitor serial checks of perfusion via mucous membrane color (should be less pale), pulse quality (should get stronger), extremity temperature, lactate levels (should go down), and mentation. We will often give a CRI of fresh or fresh frozen plasma from a well-vaccinated adult dog to attempt to augment “immunity” and some have advocated giving serum from a vaccinated adult subcutaneously. Frequent electrolyte and BG checks are essential with supplementation as needed. Warmth and nutrition are addressed as well.

Septic neonates that have been adequately fluid resuscitated may benefit from inotropic support. Due to variations in the maturity of the autonomic nervous system all inotropic drugs need to be individually tailored to each animal. Acceptable endpoints of perfusion include decreases in lactate levels, increases in extremity temperature and improvement in attitude. Ideally a C&S of the area of concern will be submitted before beginning antibiotics. Broad-spectrum antibiotics may be required if the source of infection cannot be identified. 1st generation cephalosporins are a good choice in the neonate and provide coverage for gram positive and some gram-negative organisms.

Oxygen therapy should be kept below an  $\text{FiO}_2$  of 0.4 to avoid oxygen toxicity, which is even more of a concern in neonates than in adults. Excess oxygen supplementation can cause retrolental fibroplasia, which can lead to permanent blindness.

Differences in coagulation indices (lower concentration of endogenous anticoagulants protein C&S and antithrombin) may predispose neonates to a pro-thrombotic state. Higher levels of unfractionated heparin and low molecular weight heparin are needed in human neonates and pediatric patients.

### **Respiratory Distress of the Newborn**

#### *Causes of Respiratory Distress*

The respiratory distress encountered at birth may be due to pulmonary hypertension, decreased surfactant levels (prematurity), aspiration of meconium, or excess fluid in the airways. Congenital defects may cause persistent pulmonary hypertension and respiratory distress that is refractory to treatment.

#### *Emergency Treatment*

Emergency treatment of a newborn in respiratory distress includes reversal of any drugs that were used during anesthesia if a cesarean section was performed. Bulb suctioning of the airways can help clear out any accumulated fluid. Aggressive suctioning of the airways (i.e., with a suctioning device) should be avoided as this can cause a vagal response or laryngospasm. Gentle rubbing of the neonate all over can also help stimulate respirations. Shaking or hitting the newborn is contraindicated and can cause loss of surfactant among other complications. Doxapram hydrochloride can be given under the tongue to stimulate respirations in a newborn with no respiratory drive.

#### *Physiology of Respiratory Distress*

At birth, physical expansion of the lungs causes release of prostacyclin, which increases pulmonary blood flow through pulmonary vasodilation. Nitric oxide contributes to pulmonary vasodilation and is thought to be released in response to oxygenation. Surfactant reduces the tension of the air-fluid interface of the alveoli and prevents collapse. It is essential to reduce compliance (stiffness) and therefore the work of breathing. Surfactant is released at birth in response to lung inflation. Dramatic decreases in pulmonary vascular resistance and adequate surfactant synthesis and release are essential to neonatal survival at birth. The two most important interventions for respiratory distress at birth are oxygenation and lung expansion. These will maximize the release of prostacyclin and nitric oxide (pulmonary vasodilation, decreased pulmonary vascular resistance) and surfactant release.

Oxygen should be supplied via facemask or endotracheal tube, as adequate lung expansion is crucial for pulmonary blood flow. Lung expansion causes surfactant release and release of prostacyclin

(causes vasodilation and relaxation of pulmonary vessels). Over expansion can cause damage so it is essential to use the minimal amount of pressure for ventilation. We use an ambubag designed for pediatric use and intubate and ventilate if there are no spontaneous respirations after 45-60 seconds. The neonate should be ventilated at 25 bpm and this should be done for ~15 seconds before cardiac compressions are started.

#### *Cardiopulmonary Resuscitation in the Newborn*

Cardiac compressions are done with the thumb and forefinger on either side of the thorax and compressing a minimum of 100-120 times per minute. In a piglet model of cardiac arrest it was shown that thoracic compressions actually cause cardiac compression (-vs. the thoracic pump theory in larger animals). Intravenous access is ideal for delivery of drugs for resuscitation but intraosseous routes work well also. Neonates have a higher proportion of red marrow than adults (who have more yellow-fat marrow) making the IO route ideal in the young. When an IO catheter is placed it is essential to remove it as soon as possible. In humans, complications of IO catheters are kept to a minimum by removing them within two hours. The goal is to use the IO catheter as a bridge to increase volume and make placement of an IV catheter possible.

Epinephrine has both alpha and beta adrenergic activity and is the first line drug during cardiopulmonary arrest. It is delivered at 0.01mg/kg (the low dose) for the first 1-2 doses and then at 0.1mg/kg (the standard or high dose) for the subsequent doses. Recently vasopressin has been advocated for cardiopulmonary arrest in humans. The new standards allow vasopressin to be administered if the first two doses of epinephrine are unsuccessful. This has not been looked at in either human neonates or small animals.

Acidosis due to decreased perfusion (i.e., metabolic lactic acidosis) and decreased ventilation (i.e., respiratory acidosis) is common during CPA and ideally should be addressed by treating the primary problems (i.e., increasing perfusion and ventilation). Severe acidosis can decrease myocardial contractility, which could be critical in neonates who have a lower percentage of myocardial contractile fibers than adults. It can also blunt responses to catecholamines, which, again is critical in neonates who have a lower percentage of sympathetic fibers in their myocardium compared to adults. The use of buffers (e.g., sodium bicarbonate) is controversial because they increase sodium levels, cause hyperosmolality, can cause paradoxical CNS and intracellular acidosis, and increase carbon dioxide. If ventilation and perfusion are adequate, the addition of buffers is suggested after 10 minutes of cardiac arrest. Sodium bicarbonate is recommended at 0.5 – 1.0 mEq/kg in humans with CPA.

Glucose is the main energy substrate of the neonatal brain and myocardium and should be monitored frequently during an arrest and supplemented as needed. Ionized calcium has been shown to be low in human neonates. Neonates also have an increased requirement for calcium for contractility compared to adults. Calcium is not recommended for CPA in human neonates, however.

### **Head Trauma**

#### *Difference in Neonates*

Pediatric and neonatal children have a higher percentage of diffuse brain injury compared to adults and this is thought to be due to their greater head to torso ratio. The neonatal brain also has higher water content, lacks complete axonal myelinization, and may be more susceptible to hypoxia and hypotension than adults. It may be more susceptible to apoptosis and delayed cell death during head trauma than adults. As in adults, the goal with head trauma is to improve oxygen delivery, decrease intracranial pressure (ICP), and maximize cerebral perfusion pressure (CPP). Human children have a lower ICP as well as a lower MAP compared to adults. Puppies have a lower MAP and since;  $CPP = MAP - ICP$

It can be seen that MAP must be kept high, and ICP kept low in order to maximize CPP. One of the most essential treatments for head trauma victims is appropriate fluid therapy, keeping the systolic BP above 90mmHg is suggested and this has been associated with improved survival. Since CPP depends on adequate cardiac output, systemic perfusion and adequate ventilation these should be optimized in head trauma victims. Both hyper- and hypoventilation should be avoided in favor of normocarbia. Hyperventilation to reduce the PaCO<sub>2</sub> to less than 35mmHg may be helpful in an emergency situation with impending signs of brain herniation. The resulting vasoconstriction can decrease the CPP leading to decreased oxygen delivery and hypoxia. Once volume has been addressed (i.e., fluid therapy) vasopressor are often administered in humans if MAP is still low.

### *Seizures After Head Trauma*

Seizures after head trauma appear to be more common in children than in adults and can occur in children with minimal brain damage. Elevation of the head to 30 degrees has been suggested but this must be done without compressing the jugular veins (i.e. using a tilt table or a foam wedge). The habit of placing a rolled up towel under the neck to elevate the head is potentially dangerous, as compression of the jugular veins has been shown to increase ICP. No jugular catheters or neck bandages in head trauma patients.

### *Detection of Increased Intracranial Pressure*

In humans, measurement of ICP can be made directly but this is impractical in most veterinary situations. In adult dogs the Cushing's reflex can be helpful to gauge increasing ICP. When ICP increases, the systemic blood pressure rises, and as a response the heart rate decreases. Seeing a bradycardic, hypertensive head trauma animal is highly suggestive of increased ICP. Unfortunately this has not been looked at in neonatal and since their autonomic nervous system is not mature until 9-10 weeks of age there is good reason to believe that this sign might be unreliable in these patients.

In summary, the magnitude of head trauma can be difficult to assess in pediatric patients. Treatment involves optimizing systemic blood pressure using fluids and vasopressor as needed, raising the head 30 degrees without compression of the jugular veins, and optimizing oxygen and ventilation.

### **Conclusion**

Many monitoring, laboratory and pharmacological data differ dramatically in neonates compared to adults of the same species. Due to these unique characteristics awareness of these variations is essential in monitoring and treatment of the neonatal animal during times of hypovolemia, shock, and sepsis.

Anil AB, Anil MA, Yildiz M, et al. The importance of microalbuminuria in predicting patient outcome in a PICU. *Pediatr Crit Care Med* 2014;15:e220-d225

Additional References available upon request