Neonatology

Sepsis and septic shock

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Septic shock is the most frequent killer of neonates in our NICU population. The terminology used to talk about sepsis and septic shock can be confusing. Before we had a good understanding of the pathogenesis of sepsis and septic shock we used to think in terms of either bacteria or bacterial toxins circulating in the blood causing direct damage. Thus the term septicemia originally meant the presence of bacteria or toxins in the blood causing damage to the host. We now know that, although bacterial toxins can cause some direct tissue damage, most of the response seen in sepsis and septic shock is caused by a cascade of intrinsic mediators released in response to the presence of bacteria or their toxins resulting in reactions mediating the host's attempt to destroy the bacteria and tissues infected by the bacteria. This cascade of pro-inflammatory mediators and procoagulants is called systemic inflammatory response syndrome (SIRS). As with most cascade of mediators in the body, there is a balancing cascade of anti-inflammatory mediators and anticoagulants called the compensatory anti-inflammatory response syndrome or CARS. We also now realize that the SIRS reaction is not solely a response to bacteria, but may be induced by viral, fungal or protozoal infections, extensive trauma, extensive hypoxic ischemic disease and certain drugs (primarily antineoplastic). In general, the SIRS response is appropriate for the initiating situation. That is there may be local invasion of a pathogen and through the SIRS response the body is able to not only kill the pathogen but destroy damaged tissues and protect the host from infection. However when this reaction goes beyond the local site of invasion and if it is not properly balanced by CARS, it may get out of hand and result in damage to many vital organs leading to a condition called multiorgan dysfunction syndrome or MODS. In many cases, MODS leads to death. In other situations, occasionally the CARS response may be too vigorous blocking the host's effort to kill the pathogens and resulting in an overwhelming infection. So this carefully balanced system that is in place to protect the host can occasionally malfunction and result in devastating disease in the host. This devastating disease is septic shock.

The most common causes of septic shock in our neonates are bacterial infections (both gram negative and gram positive) and viral infections. Also, a proportion a very severely affected hypoxic-ischemic foals may develop SIRS and die of septic shock. By far the most commonly found bacteria resulting in sepsis (infection) in foals is *E. coli* but other pathogens include *Enterobacter*, *Enterococcus*, *Staphylococcus*, *Actinobacillus*, *Klebsiella*, *Acinetobacter*, *Streptococcus*, *Pasteurella*, *Salmonella*, *Clostridia*, *Pseudomonas* and *Bacillus*. Veterinarians seemed fixated on endotoxin as the cause of septic shock and

SIRS. But besides endotoxin, which is a powerful inducer of SIRS, gram negative pathogens also contain formyl peptides, exotoxins and proteases all of which can initiate the SIRS response. Gram positive pathogens contain exotoxins, enterotoxins, hemolysins, petidogalycans and lipoteichoic acid all of which may also initiate SIRS. Although these toxins may cause direct tissue damage their major effect is stimulating the release of pro-inflammatory cytokines (the spark for the fire). Toll-like receptors primarily on macrophages recognize the presence of these initiators beginning the cascade with the initiation of the intrinsic and acquired immune systems. These initiating cytokines in turn, cause the release of a massive cascade of mediators (the fire) resulting in the pathophysiologic changes characteristic of SIRS and septic shock. At the same time, the CARS response is stimulated releasing anti-inflammatory mediators (the damper) that modulate the inflammatory response.

The cardiovascular effects of the inflammatory mediators include an increase in heart rate, an increase in cardiac output, a decrease in systemic vascular resistance (arteriolar tone decreases resulting in hypotension and venous tone decreases resulting in splanchnic venous pooling), and an increase in pulmonary vascular resistance (can result in pulmonary hypertension). Despite the increase in cardiac output there is tissue hypoperfusion, an increase in lactate production and a decrease in oxygen utilization. The problem is not perfusion but distribution of perfusion. The maldistribution results in inappropriate hyperperfusion of some areas and inappropriate hypoperfusion of others. There is also decreased sensitivity to catecholamines caused by circulating vasodilator substances which counteract catecholamines and cause adrenergic receptor down regulation. There is a loss of microvascular autoregulatory mechanisms secondary to microvascular damage. There also seems to be altered tissue oxygen metabolism. There is the apparent inability of systemic tissues to extract oxygen from the blood, even though the oxygen delivery appears to be adequate. The tissues function as if they are oxygen starved and begin anaerobic metabolism with production of lactic acid. This has been termed a hypermetabolic state giving rise to the descriptive phase "hyperdynamic shock syndrome." It is not truly understood whether the tissues are hypermetabolic or whether there is a block in oxygen utilization, but current evidence points to mitochondrial dysfunction. At this point cellular damage develops which is often irreversible. It can be secondary to the initiators (e.g. endotoxin) but often is caused by local mediators (NO, TNF, etc.) released in response to the inflammatory cascade. The major underlying theme is a problem of distribution of blood flow. Thus septic shock is sometimes called distributive shock because of the maldistribution of blood flow resulting in the dilation of most vascular beds and constriction of others.

Portals of entry of bacterial pathogens include the GI tract, the respiratory tract (secondary aspiration), the placenta (secondary to *in utero* placental infections) and the umbilicus. The umbilicus is overrated as a portal of entry. The

gastrointestinal tract, through translocation of bacteria, is probably the most important portal of entry. Factors which predispose to sepsis include prematurity, hypoxic ischemic disease, hypothermia, failure of passive transfer, immature or suppressed immune response, stress, poor nutrition and poor husbandry. Once the pathogens enter the neonate's body the infection may localize resulting in pneumonia, enteritis, arthritis, osteoarthritis, meningitis, omphalitis or may remain generalized (septicemia).

Early signs of sepsis include loss of suckle, fever or hypothermia, lethargy, weakness and injected scleral or oral membranes. Other signs include tachycardia, tachypnea, petechia of the oral, scleral, or aural membranes, hyperemia of the coronary bands (coronitis), linear dermal necrosis (LDN -- necrosis of the skin often over the hock in a linear pattern), either increased or decreased capillary refill time and finally shock. These signs are caused by over activation of the inflammatory response resulting in showers of inflammatory mediators. The inflammatory reaction can cause damage to the GI tract, lungs, CNS or kidneys. In the GI tract there may be a breach of the intestinal barrier and translocation of bacteria into the submucosa. In the lungs damage can be widespread and result in acute respiratory distress syndrome (ARDS) and severe respiratory failure, resulting in poor oxygen loading of the blood. In the CNS there may be changes in vascular permeability interfering with normal blood brain barrier function resulting in cerebral dysfunction. There can be decreased renal blood flow resulting in prerenal azotemia and later acute tubular necrosis resulting in renal failure. This may be mediated either by hypotension or damage to the microvasculature. All tissues may be affected by hypoxic ischemic damage secondary to hypotension, poor perfusion and poor oxygen deliver which is exacerbated by poor oxygen loading of the blood in the lungs. In all tissues occlusion of vessels because of adherence of platelets and neutrophils to damage endothelium and formation of microthrombi as a procoalulant response results in regional hypoxic ischemic damage, even if perfusion and regional oxygen delivery is returned through therapeutic interventions.

Early release of inflammatory mediators results in fever, tachycardia, tachypnea and vasodilatation (resulting in warm skin). All of these may be transient and represent an appropriate and well controlled SIRS response to an infection. However if the response is not well controlled and hypoperfusion develops, further signs will be somnolence, falling asleep on their feet (foals standing with her head dropped and seemingly asleep) and decreased urine output. This change in mental attitude that we often called depression is probably associated with hypoperfusion of the brain and is a clear indication for therapy with intravenous fluids. Somnolence also may be caused by increased production of neurosteroids which help protect the brain from excitatory neurodamage produced by inflammatory mediators leaking through a compromised blood-brain barrier. Another early finding is bounding pulses with a wide pulse pressure representing increase cardiac output and increased systemic vascular

resistance. The extremities will become cold as blood is redirected away from them to other tissues. Initially the pulses will still be strong and bounding despite the cold extremities. However as the distribution of blood flow becomes confused (maldistribution) the extremities will become less cold but pulses will be weak and CRT will be prolonged. Animals respond best if you can treat them when their pulses are still strong, arterial blood pressures are still high and before they begin to slip into the latter stages of shock. The homeostatic mechanisms will begin to fail and hypotension will develop. As this occurs the pulse pressures will narrow so the pulses do not feel bounding but instead become weaker. Despite this there will be extreme tachycardia and tachypnea. The neonate will become recumbent and nonresponsive. This is followed by development of hypoxia and metabolic acidosis resulting in direct myocardial depression and decreased cardiac out put finally followed by death.

Treatment

The keys to intervention in sepsis and septic shock are treating the underlying infection, providing hemodynamic support, providing support for multiorgan dysfunction and the associated metabolic crisis and attempting to block pro-inflammatory mediators.

Treating the underlying infection: Although septic shock may be caused by a number of different etiologic possibilities, most of the cases of septic shock seen in farm animal neonates are secondary to bacterial infections. Because there's no time to wait for definitive diagnosis, overwhelming bacterial infection should be anticipated and antimicrobial therapy initiated. Antimicrobials should be selected based on sensitivities from recent isolates from other neonates presenting in your practice. *In utero* infections are also possible and when the epidemiologic and clinical findings point towards a virus consideration to early use of acyclovir should be made. In all cases the neonate may benefit from hyperimmune plasma transfusion providing not only specific antibodies but nonspecific immune stimulants and cofactors.

The most commonly used antimicrobials include penicillin and an aminoglycoside (usually amikacin). Another good choice is a third generation cephalosporin with or without an aminoglycoside or a potentiated penicillin with or without an aminoglycoside. The choice is usually based on experience in the recent past with pathogens isolated from similar cases in the practice, especially *E. coli* which is the most commonly associated pathogen.

Hemodynamic support: The goals of hemodynamic support are to improve perfusion, to optimize cardiac output and increased systemic oxygen delivery as indicated by decreasing the blood lactate levels. In the treatment of a neonate presenting in septic shock, aggressive fluid therapy is very important. Crystalloids or colloids may be used although in our practice primarily crystalloids

are used. My fluid of choice in cases where I have not had extensive blood work is Normisol R.® A push of 20 ml/kg over 10 to 20 minutes will help expand plasma volume. This limited bolus will allow for a discrete period to reassess the patient to decide whether more fluids are needed and will help minimize fluid overload as may occur in cases where fluids are given by rapid administration and forgotten until later on in the clinical course (not slowed after volemia is returned). Reassessment of the patient after every bolus includes looking for an improvement of blood pressure, looking for improvement in peripheral perfusion as indicated by extremity temperature, feeling the peripheral pulses for improvement, watching for urine production and detecting an improvement in mental status. As mentioned above, plasma therapy can be very helpful in the host's ability to fight off sepsis. Plasma, a colloid, may be used as a volume expanding fluid as well although in most cases it is frozen and requires some time to thaw. Whole blood is probably the best replacement fluid and if there is accompanied anemia it is important to transfuse the neonate. Above all the clinician needs to guard against over hydrating the patient and should constantly ask himself/herself if the volemia goals have been met and fluid therapy should be moderated. Once fluid goals are reached, fluid rate should be slowed to maintenance level. If fluid resuscitation does not result in a marked improvement in perfusion pressures and inotropes should be added to therapeutic regime.

The most useful inotrope/pressor drugs are dopamine, dobutamine, norepinephrine and epinephrine. Dopamine is a mixed pressor/inotrope and is relatively inexpensive. Dobutamine is an excellent inotrope but lacks pressor activity at low infusion rates. Norepinephrine is an excellent pressor but has little inotrope activity. Combining dopamine and dobutamine or dobutamine and norepinephrine results in a good therapeutic combination. Epinephrine is a mixed pressor and inotrope and also can be quite useful in these situations. When giving pressor/inotropes there must be an accurate continuous infusion. An accurate infusion pump is a must. Also the clinician should continually remind himself/herself that the therapeutic goal is to increase perfusion not "get good blood pressure numbers." The inotrope effect is the most important, increasing cardiac output when the heart has passed through the hyperdynamic stage of septic shock and has begun to fail. Overzealous use of pressors may negate the inotropic effect and should be guarded against. Hopefully with the combination of an inotrope and pressor there can be some correction of the maldistribution of blood flow in septic shock. Each patient becomes a pharmacokinetic experiment and the infusion rates need to be titrated individually. A major negative side effect of these drugs are arrhythmias, especially tachycardia. If this develops, the drug choice needs to be modified.

Vasopressin, a non-adrenergic naturally occurring pressor also know as antidiuretic hormone (ADH), has been found to be very useful in septic shock. Patients with refractory septic shock have been found to have a deficiency of this hormone. When administered at a very low dose, so that blood levels are

returned to normal, refractory shock may respond to either endogenous adrenergic tone or exogenously administered adrenergic drugs. The low dose results in replacement therapy (as apposed to pharmacologic therapy, when larger than physiologic doses are used) and thus a more natural response with hopefully better distribution of perfusion. Using vasopressin along with an inotrope (usually dobutamine) is currently my favorite drug combination for cardiovascular support in septic shock.

Support for other organ systems during sepsis: Nutritional support is very important during sepsis. Sepsis is associated with hypermetabolism and malmetabolism. Neonates that are septic may either be hyperglycemic or hypoglycemic. Hyperglycemia may be mediated through catecholamines stimulating glycolysis and catecholamine mediated insulin resistance. In general, I feel that the hyperglycemic individual is starving their tissues. In such cases the use of an intravenous insulin drip sometimes can modify the tissue's response to glucose and allow better glucose metabolism. Although much of the insulin mediated enhancement of glucose utilization is occurring in the muscles, I feel that starving the muscles has a significant negative effect on overall systemic metabolism and allowing the muscle access to glucose can be important. Hypoglycemia is very commonly associated with hypermetabolism and sepsis. Sometimes the neonate requires very large glucose infusion rates to maintain blood glucose in an acceptable level. Glucose infusion rates generally are begun at 4 mg/kg/min and increased until the glucose is stable. In severe cases infusion rates between 10 and 20 mg/kg/min are not unusual. In the worst-case scenario, as sepsis progresses, the neonate will become glucose intolerant and then lipid intolerant and finally fails to even catabolize proteins. If this occurs, it will potentiate and speed the failure of many body systems.

Although supporting hemodynamics will help optimize oxygen delivery to tissues, optimizing pulmonary transfer of oxygen is also necessary. There are many changes that occur in septic shock which interfere with oxygen uptake in the lungs including the development of pulmonary hypertension with associated right to left shunting in the neonate and significant mismatching secondary to abnormal vascular control in the lungs. Another consideration is that at least 25% of oxygen consumption during septic shock in a patient in respiratory distress is used to support respiration. If the work of breeding can be minimized and the matching of ventilation to perfusion optimize then the neonate has a better chance of overcoming septic shock and not suffering from a lack of oxygen delivery. All neonates suffering from septic shock should be placed on intranasal oxygen to decrease the work of breathing and optimize gas transport. Early in the course of the disease consideration should be given to ventilation which will decrease the work of breeding, increased cardiovascular function and make early respiratory failure easier to manage and possibly improve outcome. When ventilated, a modest PEEP should be used to decrease the work of breathing and airway resistance and decrease hypoxia and the need for high F_{IO_2}. Inhale

nitric oxide may be useful in reversing the pulmonary hypertension that is secondary to septic shock.

Blocking pro-inflammatory mediators: During the past two decades there has been much excitement about developing specific mediator blockers in attempts to prevent the devastation that accompanies septic shock. Intuitively it makes sense that since the clinical signs of septic shock are mediated through a cascade of pro-inflammatory substances, that if the initiators of the cascade can be blocked then the disease should be modified or even prevented. More than 15 specific antimediator strategies have been developed and shown to be highly successful experimentally in animal models. Unfortunately they have been uniformly unsuccessful when used in large clinical trials in man. In fact, some of the most promising therapies in experimental models have resulted in increased fatality rates in large human trials resulting in early termination of the studies. Studies have shown some positive results using activated protein C, however, success has been somewhat limited and fatal complications can occur. Most recent studies contradict the initial findings suggesting that activated protein C is not the answer and recently it has been voluntarily removed from the market worldwide. Although our large animal species may be different than humans, I've always thought of large clinical trials in human medicine as excellent experimental data for us. The problems encountered in the human trials are very likely transferable to our situation. The experimental models are, always by necessity, designed using a discrete initiator of SIRS to study the blockade of a mediator. Unfortunately in real-life there's not one initiator. Most often the trials involve endotoxin but as mentioned earlier there are a number of bacterial products that begin this cascade of events. Other trials are focused on the initial mediators which spark the fire of the reaction. However these mediators likewise are multiple. Most recently it is been realized that when attempting to block the SIRS reaction early in the cascade, often the CARS responses blocked as well. Unfortunately the SIRS cascade may not be blocked completely resulting in a reaction which is not balanced properly by CARS. If the CARS responses are not stimulated because of blockade of early mediators of SIRS, disastrous results can be expected. With our current knowledge of the complexity of the cascading events surrounding septic shock it's clear that timing is very important and because of the nature the response and complexity it is easy to imagine that the outcome could vary dramatically if the timing is off. It is also hard to imagine that blocking a single mediator would result in complete blockage of the cascade. So there's no silver bullet that will prevent the cascade from developing and save our patient. Although it has been shown to fail in human trials, the most commonly used antimediator therapy in veterinary medicine is hyperimmune plasma with a high anybody level to endotoxin. Other commonly utilized antisepsis drugs include flunixin meglumine, pentoxifylline, DMSO, polymixin B and steroids. Perhaps in the future as the interactions are better understood and the factors affecting timing may be predicted in clinical cases, antimediator therapy will be met with more success.