Everything You Need to Know about Intensive Care Mini Series

Session Two: The Septic Patient

Alessandra Mathis DVM CertVA DipECVAA MRCVS

European Specialist in Veterinary Anaesthesia and Analgesia

RCVS Specialist in Veterinary Anaesthesia

Sepsis

Sepsis is a life-threatening condition caused by an infection leading to dysregulated host response and, too often, death. The mortality rate in human affected by sepsis is of about 1 in 4. In small animals, the mortality rate is believed to be similar.
Treating a patient in sepsis is very challenging and often unrewarding. Because of the lack of consensus on what treatment approach is effective, international guidelines were published by a panel of experts. The Surviving Sepsis Campaign was first published in 2004 and after this reviewed every 4 years, with the latest review being published in 2016. It is important to understand that guidelines do not replace the clinician's decision-making capabilities.

Definitions:

- **SIRS:** Systemic Inflammatory Response Syndrome: the patient presents clinical signs of systemic inflammation (see Table 1) in response to infectious or non-infectious insults (including trauma, pancreatitis, burns, neoplasia…).

Table 1. Systemic Inflammatory Response Syndrome Criteria for Dogs and Cats

Species	Dogs	Cats
Temperature °C	< 37.2, > 39.2	< 37.8, > 40
Heart rate (bpm)	> 140	< 140, > 225
Respiratory rate (bpm)	> 30	> 40
WBC X 10^3/µl	<6, >19	< 5, > 19

- **Sepsis:** life threatening organ dysfunction caused by a dysregulated host response **to infection**
- **Septic shock**: a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality

Common causes of SIRS are trauma, burns, pancreatitis, major surgery, immune mediated disease and neoplasia. Common causes of sepsis are septic abdomen, bite wounds, pyothorax, pyometra and parvoviral enteritis.

Pathophysiology

The pathophysiology of sepsis is complex. Normally an insult would cause an inflammatory response which is localized to the area. This inflammatory response will cause release of inflammatory mediators and acute phase proteins. Sometimes this localized response can become systemic. Physiologically the organism will produce a secondary anti-inflammatory response which, if excessive will lead to immunosuppression and immunoparalysis. Sepsis is a pathological disrupted equilibrium in between the physiological pro-inflammatory and anti-inflammatory responses of the organism.

Clinical findings

Clinical signs of sepsis are not very specific. Signs of SIRS (see table above) should be present and other signs can include depression, vomiting, diarrhoea, dehydration, hypovolaemia, tachy mucous membranes, weak or thready pulses and other signs of shock if septic shock is present.
Blood work is also very unspecific. Neutropaenia or neutrophilia with a left shift may be present. Often albumin is decreased.

Blood glucose may be decreased (more often) or increased. Electrolyte imbalances may be present and other blood work abnormality related to the underlining disease may be present as well.
Lactate, result of anaerobic metabolism, is most commonly an indicator of hypoperfusion. Lactate is also produced in other conditions including hypoxia, accelerated aerobic glycolysis, liver failure …. Regardless of the source, increased blood lactate is associated with poorer outcome, mostly if high levels persist after fluid therapy.

Initial resuscitation

If not present an IV cannula should be placed and IV fluid therapy started as soon as possible. The priority is to restore oxygen delivery to the tissues as soon and as efficiently as possible.

Oxygen delivery (DO_2) to vital organs:

$$DO_2 = CO \times C_aO_2$$

Where:

CO: cardiac output

C_aO_2 arterial oxygen content

$C_aO_2 = 1.36 \times [Hb] (\%S_aO2) + (0.003) P_aO_2$

Initial resuscitation is a medical emergency and should be started immediately. The guidelines state that at least 30 ml/kg of IV crystalloids should be administered within the first 3 hr and additional fluids guided by frequent reassessment of the haemodynamic status.
An initial target MAP of 65 mmHg must be reached which may require the use of vasopressors.
Lactate levels should be normalised as soon as possible.
What fluid to use for this purpose will depend on the underlining cause.
Hartmann's is a balanced isotonic solution containing potassium in similar amounts that are found in the plasma. This solution also contains lactate which is metabolised to bicarbonate in the liver and counteracts acidosis (often present in septic patients)
As with all crystalloids, after 1 hr only 1/3 of the volume administered remains into circulation. Because of the decreased albumins and increased capillary leakage present in septic patients, the use of crystalloids may lead to increased interstitial accumulation of fluids.
Saline 0.9% is another isotonic crystalloid (hence will cause the same problems mentioned for Hartmann's) but it is also hyperchloraemic compared to plasma and may cause/worsen acidosis.
Hypertonic saline has a very high osmolality, shifting water very rapidly and efficiently from the intravascular space with consequent intravascular expansion. This effect is transient and lasts approximately 30 minutes. Hypertonic saline also increases cardiac output and tissue perfusion hence is recommended in case of hypovolaemic shock but its use must be followed by the use of isotonic crystalloids.
Regarding fluids, the guidelines suggest that crystalloids should be used as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement. Albumin can be administered in addition to crystalloids when patients require a substantial amount of crystalloids
The guidelines recommend against using **hydroxyethyl starches (HES)** in septic patients. These are fluids containing macromolecules and will increase colloid osmotic pressure and intravascular volume for a more prolonged period of time compared to crystalloids. The best known HES is Voluven® (Fresenius Kabi). This particular fluid has shown to have major benefits in hypo-proteinaemic patients, patients with capillary leakage or who wouldn't benefit from an "interstitial" crystalloid overload. In the latest studies looking at goal directed fluid-therapy, voluven was better than crystalloids to increase intravascular volume and optimise CO. The reason why the guidelines recommend against HES is because in 3 large trails a clinical in human patients a clinical benefit of voluven could not be demonstrated and actually there was ample evidence of harm where the patients in the voluven group presented a higher incidence of need of renal replacement therapy and 28 days mortality rate. A drug alert was issued in June 2013 and in October 2014 the following recommendations were issued:

- Because of risk of kidney injury and mortality, HES solutions must no longer be used in patients with sepsis or burn injuries or critically ill patients
- HES solutions may continue to be used to treat hypovolaemia caused by acute blood loss. However, the doctor should monitor the patient's kidney function after HES administration

Human serum albumins are quite expensive and can cause anaphylactic reactions in veterinary patients. These reactions can be immediate or delayed (up to three weeks).
Independently from the fluid chosen for initial resuscitation, what counts is that the status of the patient and the effects of the fluids are re-assessed constantly and the patient does not become fluid overloaded.

Although a distinction in between blood pressure and blood flow to organs should be made, with the latter being more important to life than the first, it is still important to maintain blood pressure within limits which will allow the major organs to 'autoregulate' the blood flow they receive.
Blood pressure can be measure in several ways, but the invasive measurement remains the gold standard, being more reliable and continuous. If possible an arterial catheter should be placed in every septic patient.

Antimicrobial therapy:
The Surviving Sepsis Campaign suggests that:

- Administration of IV antimicrobials must be started as soon as possible after recognition and within 1 h of sepsis or septic shock
- If the cause of sepsis is unknown, empiric broad spectrum therapy - with one or more antimicrobials – should be instituted to cover all likely pathogens. This empiric therapy should then be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement noted
- The guidelines recommend against sustained systemic antimicrobial prophylaxis in patients with SIRS of non-infectious origin (pancreatitis, burns.)
- The dosing of the antibiotics is to be optimised based on accepted pharmacokinetics and pharmacodynamics of those drugs in critically ill patients
- Empiric combination therapy (using at least two antibiotics of different antimicrobial classes) should be aimed at the most likely bacterial pathogen
- Treatment duration of 7-10 days should be adequate for most serious infections.

If possible cultures should be made before starting antimicrobial therapy, but in the veterinary world it is unrealistic to expect these to be back within the hour. Hence, if the pathogen is unknown a four quadrants therapy should be started as soon as possible, taking into consideration

- The location of the infection
- The ability of the antibiotic to penetrate the site
- Suspected local bacterial flora
- Previous exposure to antimicrobials

Bactericidal antibiotics should be preferred to bacteriostatic ones.
A very good guide to veterinary antibiotic treatment based on the different body systems can be found at: www.bsava.com/Portals/0/resources/documents/PROTECT_Poster_Nov_2014_2916.pdf

Analgesia
Should be titrated to effect, administered IV if possible and pure mu agonist should be preferred to other drugs in case the patient may require surgery. It is advisable to start with low doses and increase if required.
Drugs used for a septic patient could include one or more of the following:

- Methadone 0.1 mg/kg IV increments - up to 0.4 mg/kg IV q 4-6 h
- Fentanyl CRI 0.1-0.5 mcg/kg/min
- Lidocaine CRI (dogs) 25-50 mcg/kg/min
- Ketamine CRI 1-3 mcg/kg/min
- Paracetamol 10 mg/kg IV

NSAIDS should not be administered until the patient is no longer at risk of hypovolaemia or hypotension and until the kidney function of the patient has not been investigated.

Vasopressors/inotropes
If the patient is not responsive to fluids but remains haemodynamically unstable then pressors and/or inotropes should be considered
In veterinary medicine a consensus has not been reached regarding which drug is better.
In human patients, the guidelines recommend:

- Norepinephrine as a first drug of choice
- Addition of vasopressin or epinephrine to increase the MAP to target or to decrease the amount of norepinephrine
- Dopamine as an alternative in highly selected patients (low risk tachyarrhythmia or bradycardia)
- Against low dose dopamine for renal protection
- Reserve dobutamine for patients with persistent hypoperfusion despite adequate fluid loading and use of vasopressors
- Reduce or discontinue any drug in the face of worsening hypotension or arrhythmia

- All patients requiring a vasopressor should have an arterial catheter as soon as practical if resources are available

Drug	Receptor activity			Effect on				
	β_1	β_2	α_1&α_2	Contractility	HR	CO	Vasomotor tone	BP
Norepinephrine	+	0	+++	⇧	~	~	⇧⇧⇧	⇧⇧⇧
Epinephrine	+++	+++	+++	⇧⇧⇧	⇧⇧⇧	⇧⇧	⇧⇧⇧	⇧⇧⇧
Dobutamine	++	+	+	⇧⇧⇧	⇧⇧	⇧⇧	🡻	~
Dopamine	++	+	+	⇧⇧	⇧⇧	~	⇧⇧	⇧⇧
Phenylephrine	0	0	+++	0	🡻	🡻	⇧⇧⇧	⇧⇧⇧
Vasopressin	0	0	0	0	🡻	🡻	⇧⇧	⇧⇧
Ephedrine	+	+	+	⇧	⇧	⇧	~	⇧

Different drugs and their effects on receptors are listed in Table 2.
Table 2. Vasopressors and Inotropes and their receptor activity.

As mentioned earlier, flow is the most important factor. Hence a drug as phenylephrine causing vasoconstriction and decreased cardiac output will increase blood pressure but may decrease blood flow to organs such as the gut.

Norepinephrine:
- Increases MAP due to vasoconstriction
- Has little effect on HR
- Cause a slight increase in contractility
- Dose CRI 0.1 – 2 mcg/kg/min

Epinephrine:
- Increases HR and lactate
- Decreases splanchnic perfusion (up to 48 hr in humans)
- Can cause tachyarrhythmias
- Dose: CRI 0.05-1 mcg/kg/min

Dopamine:
- Failed to normalise BP in up to 40% people with hypotension
- Causes a higher incidence of tachyarrhythmia in people
- Had a worse outcome in shock human patients when compared to norepinephrine
- Cats and dogs are different from people and dopamine is widely used and effective
- Dose 5-20 mcg/kg/min
- Dose dependent effects
    - Low dose – dopamine receptors
    - Medium dose –β receptors
    - Higher dose – α receptor

Dobutamine:
- Mostly increases cardiac contractility and HR
- The slight decrease in SVR caused, results in increased CO
- Can be used in conjunction to drugs which are mostly effective on vessel tone
- Dose 5-20 mcg/kg/min

Vasopressin:
- Acts on V1 receptors causing vasoconstriction
- Potentiates the effects of α-agonists aallowing to decrease doses used

- Is synthetized in hypothalamus, stored in the hypophysis and secreted in response to a decrease in BP, intravascular volume or increased osmolality
- Prolonged hypotension may lead to depletion of vasopressin
- Dose: 0.5-5 mU/kg/min

Phenylephrine

- Pure α-agonist
- Causes vasoconstriction and reflex bradycardia
- Increases BP but decreases CO and likely flow
- Dose: 0.5-5 mcg/kg/min

Ephedrine:

- Sympathomimetic amine which increases release norepinephrine
- Dose bolus 0.25-1 mg/kg or CRI 0.02-0.2 mg/kg/min
- Lasts 5-15 min
- Prolonged use can deplete norepinephrine stores. This phenomenon is known as tachyphylaxis

Blood glucose control:

The guidelines recommend

- A protocolised approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL (10 mmol/L)
- To target to an upper blood glucose level ≤180 mg/dL (10 mmol/L)
- Blood glucose values should be monitored every 1-2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter in patients receiving insulin infusions
- Glucose levels obtained with point-of-care testing of capillary blood may not accurately estimate arterial blood or plasma glucose values – This difference is not reported in veterinary patients

Veterinary patients are often hypoglycaemic and if too low a CRI of Hartmann's or saline 0.9% containing glucose 2.5% or 5% should be started. A dextrose 5% solution is not recommendable as once the glucose is consumed by the patient it will leave pure water behind. A custom made 2.5 or 5% solution is recommended.

If hyperglycaemia were to occur in veterinary patients this should be tolerated up to a certain level (repeated measurements > 15-20 mmol/l in dogs and cats respectively) and if treatment is required an CRI of regular insulin can be started (0.05 IU/kg/hr) but glucose and potassium should be monitored closely.

Source control

This is a fundamental step in treating patients with sepsis and should happen as soon as the patient is stable enough to undergo anaesthesia if this is necessary.

Nutrition

This is a step too often forgotten in the septic patient.

The guidelines recommend:

- Against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings in critically ill patients with sepsis or septic shock who can be fed enterally
- Early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally
- Suggest towards the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance
- Early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance

There are several ways of administering enteral food to veterinary patients (Table 3):

	Need GA	Duration	Difficulty	Diet options
Naso-oesophageal	No	3-5 days	Easy	Few
Oesophagostomy	Yes	1-3 weeks	Easy	Many
Gastrostomy	Yes	1-3 months	Difficult	Many
Jejunal	Yes	1-2 weeks	Difficult	Few
Parenteral nutrition	No	1-3 weeks	Difficult	Many

Table 3. Enteral nutrition types and some of their characteristics

Naso-oesophageal tubes

- Do not require a GA
- Are very easy to place
- Narrow gauge tubes should be used
    - 3.5-5 Fr cats
    - 6-8 Fr dogs
- Are contraindicated in facial injury, vomiting, severe obtundation, coma

Oesophagostomy tube

- Requires GA but are still easy to place, hence the GA should be of short duration
- Silicone tubes 14-19 Fr should be used and measured to the 7-8th IC space

Gastrotomy tube

- Requires GA as it is usually placed via endoscopy or surgery
- Its placement requires some skill

Jejunostomy tube

- For post-pyloric feeding (recommended in human septic patients)
- Requires GA
- Possibly reduces pancreatic stimulation
- Not used often
- Placed via surgical enterotomy but non-invasive techniques described as well

The RER should be calculated as BW x $70^{0.75}$ and the diet should be formulated according to the patient and the situation.

Parenteral nutrition should be used only in patients in which enteral nutrition is not tolerated or comatose patients with gag reflex loss

Corticosteroids:

The recommendation of the Surviving Sepsis Guidelines is against intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, intravenous hydrocortisone is suggested.

Although this is difficult to prove, during prolonged periods of stress there may be an inadequate production of cortisol in relation to an increased demand. This condition is named CIRCI – critical illness-related insufficiency. Dogs and cats which remain unresponsive to fluid resuscitation and vasopressor/inotrope therapy may benefit of 2.3-3 mg/kg/day of hydrocortisone. If no improvement is seen in 24hr then the treatment should be stopped, otherwise it can be continued for 5 days and then tapered down over 2-3 days.

Nursing care

One should not under-estimate the benefits provided by good nursing care. A comfortable bed and turning the patient every 4 hours is essential in patients which are recumbent.

In this case the person attending the patient should also consider a comfortable option for themselves (placing the patient in a cot or putting extra bedding for them if the patient is on the floor)

Mouth care and eye care, together with grooming are things one should not forget in recumbent critically ill patients

Placing a urinary catheter may help both in increasing the comfort of the patient (avoiding a full bladder) but also will allow urine output measurements. If a urinary catheter is not place the bladder should be expressed on a regular basis.

Water should be offered.

One or more IV cannulas should be placed in a clean fashion and the cannula site checked at least three times a day. These are common site of infection and bandaging may decrease external contamination.

Septic patients are often in pain and pain assessment performed with the aid of pain scoring sheets may be useful.

Even if non-ambulatory patients should be weighed at least twice a day and an increase in weight should be considered as possible fluid retention.

Critically ill patients often present with oedema, mostly if the limbs and of dependent areas. This may be due to low albumins often present in this category of patients or to fluid overload itself. If oedema is present, massage of the affected areas will help and one should check that bandaging or monitoring (mainly blood pressure cuffs) is not too tight

Other drugs:

Gastro protectants, antacids, anti-emetics and pro-kinetics can be added to the treatment of critically ill patients.

These include:

- Omeprazole 1 mg/kg IV daily
- Maropitant 1 mg/kg SQ/IV (dogs) SID
- Ondansetron 0.5-1 mg/kg SQ/IV
- Metoclopramide 0.5-1 mg/kg SQ, IV or as CRI in 24 hr

Because of the number of drugs these patients may be receiving in the 24hr, one must have organised kennel sheets and compatibility in between drugs should be checked

Last but not least, goals of care, prognosis and costs should be discussed upfront with the owners. The prognosis is often poor and the mortality rate high.

Conclusions

Treating septic patients can be very challenging, mostly if septic shock is present. Early recognition and intervention are paramount to save the patient's life.

A septic patient will require a very intensive treatment, around the clock and with multiple knowledgeable members of staff involved. If successful treatment of this type of patient can be very rewarding.