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How to Survive OOH!
Mini Series

Session 2: Top Priorities in All Emergency Patients: Shock, Fluid Therapy and Analgesia

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SHOCK, HYPOVOLAEMIA AND DEHYDRATION

Cardiovascular examination

Evaluation involves examination of the following:

- Heart rate and rhythm
- Heart sounds
- Pulse quality and rate
- Mucous membrane colour
- Capillary refill time
- (Mentation; temperature of the extremities)

The most important questions to answer are:

- Is systemic perfusion normal? Perfusion is a key concept in emergency medicine.
- Is there a murmur or gallop sound suggesting possible primary cardiac disease?
- Is there suspicion of a potentially clinically significant dysrhythmia?

Heart rate and rhythm

Normal adult range in **dogs**: 70-120 bpm

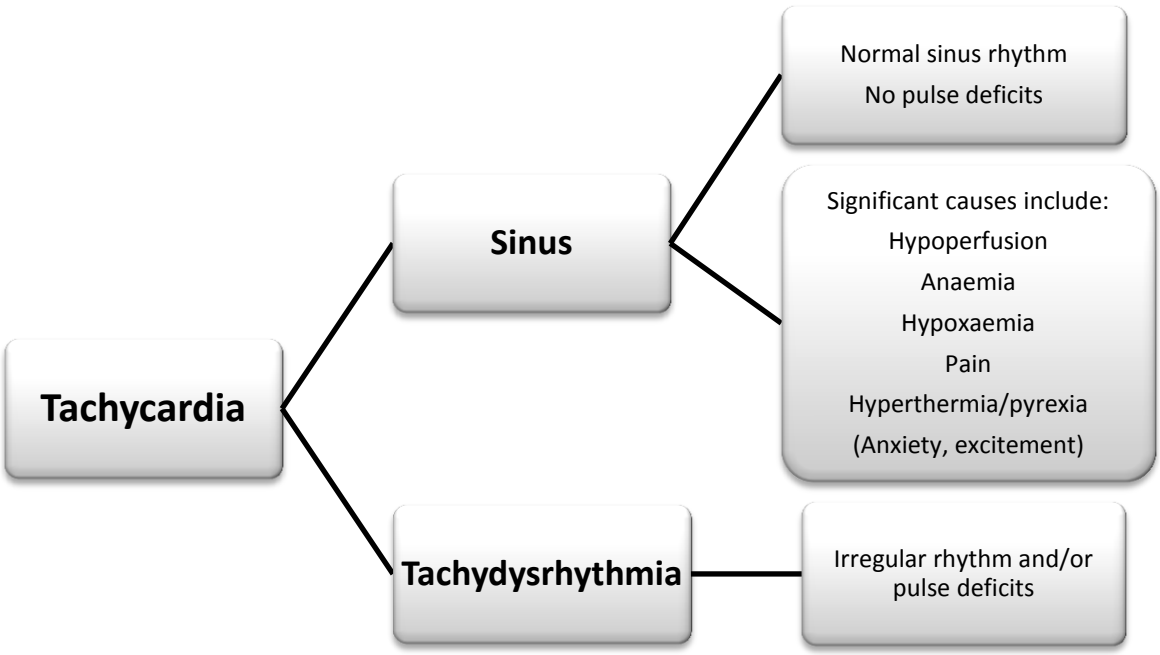
- Larger dogs usually have slower rates than smaller dogs
- Potentially affected by various other factors
- Interpret the measured HR in the context of each individual patient

In general when interpreting physical examination findings it is essential to ask not just if the measured value falls within quoted 'normal ranges', but whether it is *appropriate for the individual patient in question.*

Normal adult range in **cats**: 160-200 bpm (at initial consultation)

- More susceptible to 'stress' and much higher rates (e.g. 220-240 bpm) may be found in healthy cats

Tachycardia…



Bradycardia

Both sinus bradycardia and bradydysrhythmias considered significant. Causes include:

- High vagal tone: many causes, e.g. respiratory disease, intra-abdominal disorders
- Drug side effect: especially anaesthetic agents and (pure) opioids
- Cardiac conduction disturbances (e.g. atrioventricular block)
- Brain disease (secondary to raised intracranial pressure)
- Hyperkalaemia (e.g. urethral obstruction, Addison's disease)
- Hypoglycaemia (probably only if moderate-to-severe)

Heart sounds

Most dogs with clinically significant heart disease have a readily audible murmur.
Many cats with clinically significant heart disease have a readily audible gallop sound (third heart sound) or murmur.
Murmurs are more likely to be audible at higher rates or in the presence of greater sympathetic stimulation of the heart.
Quiet heart sounds may be due to muffling (especially from pericardial effusion; also e.g. pleural effusion, mass/organs between stethoscope and heart) but possibly also hypovolaemia.

Normal cardiac auscultation does not exclude the presence of clinically significant heart disease.

Focused cardiac ultrasound is very achievable by non-cardiologists in veterinary patients and is used for example to evaluate left atrial size as a marker of cardiac disease, to assess contractility, and to exclude pericardial effusion.

Pulse quality and rate

Arterial sites: especially *femoral* (medial aspect of proximal hindlimb) and *dorsal pedal* (metatarsal; distal to hock on craniomedial aspect).

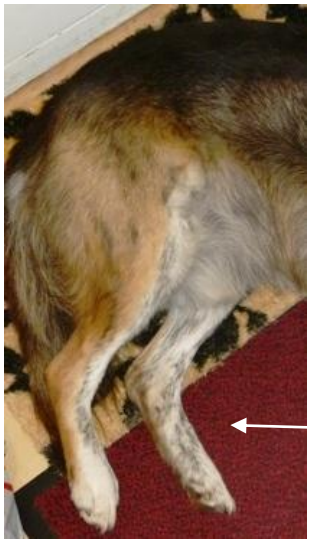
Normal arterial pulse: readily palpable and strong
Stronger or easier than normal to feel: 'bounding', 'snappy', 'hyperdynamic'

- Typically tachycardic
- Causes e.g. early shock, anaemia

Weak, very weak/'thready' or absent: e.g. later stages of shock; low output (forward) heart failure

Pulse deficit: pulse rate lower than concurrent heart rate

- Due to dysrhythmia with some heart beats unable to generate palpable peripheral arterial pulse
- Perform ECG to evaluate further



Approximate location of dorsal pedal artery

Mucous membrane colour

Normal salmon pink appearance requires there to be enough oxyhaemoglobin in enough red blood cells in the capillaries of the mucous membrane site being examined. Abnormalities are:

Pallor
Injection/congestion
Cyanosis
Other abnormalities

Pallor

Causes of:

- Poor blood flow due to vasoconstriction (e.g. common in shock; also hypothermia)
- Overall lack of circulating red cells in anaemia

Injection/congestion

Increased blood flow (hyperaemia) gives membranes that range from being pinker than normal right through to bright red
Mild cases, e.g. due to tachycardia and increased cardiac contractility in early shock
More severe cases are usually due to vasodilation and tachycardia, e.g. systemic inflammation, vasodilatory anaphylaxis, hyperthermia.

Cyanosis

Bluish or purplish discoloration of the mucous membranes or skin due to a severe decrease in the amount of oxygen dissolved in the perfusing blood.
Central cyanosis typically indicates life-threatening systemic hypoxaemia due to circulatory and/or ventilatory failure.
It may be difficult to detect if perfusion is very poor or the patient has a packed cell volume (PCV) < 15% (as > 5 g/dL of deoxyhaemoglobin is required for cyanosis to be visible).

All cyanotic patients require urgent intervention with oxygen supplementation and addressing the underlying cause if/as possible.

Other abnormalities

Icterus (jaundice) is a yellow appearance of the mucous membranes or skin due to hyperbilirubinaemia.

Petechiae (pinpoint) and **ecchymoses** (larger) are the result of superficial bleeding. They are typically due to severe thrombocytopenia, platelet function disorders (thrombopathias), or a localised or systemic vasculopathy.

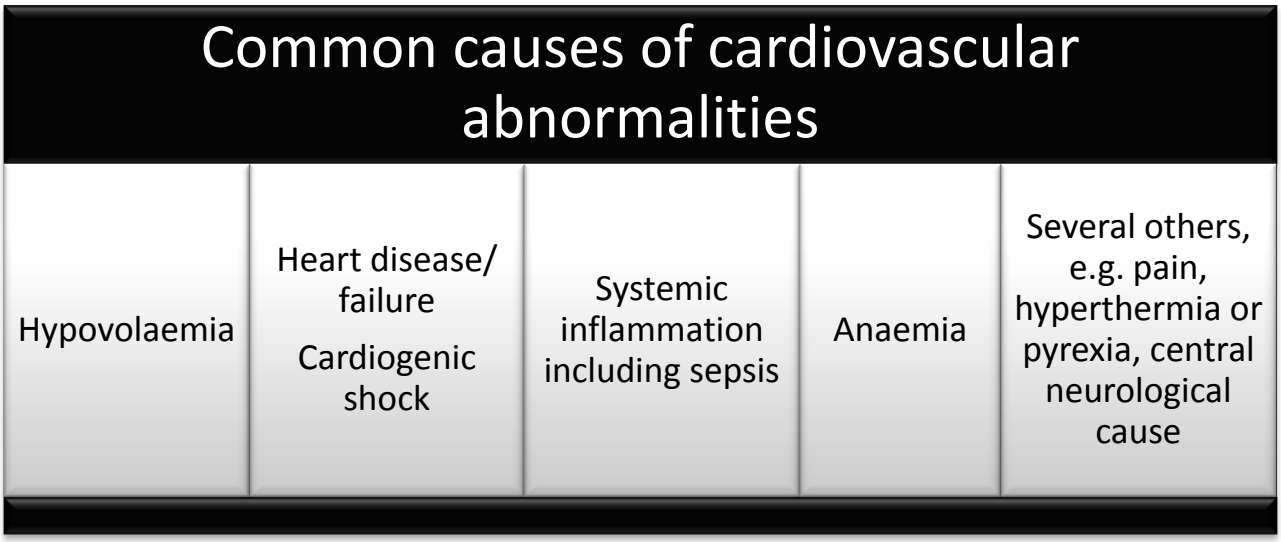
Increases in the concentration of **other types of haemoglobin** besides oxy- or deoxyhaemoglobin, e.g.

- Methaemoglobinaemia in paracetamol (acetaminophen) poisoning causes brownish discolouration
- Carboxyhaemoglobinaemia in carbon monoxide poisoning causes a cherry-red appearance

Capillary refill time

Affected by blood flow to the site and therefore varies predominantly according to whether the underlying vessels are constricted or dilated:

- Normal: 1-2 seconds
- Slow (> 2 seconds): especially in peripheral vasoconstriction (e.g. shock, hypothermia)
- Fast (< 1 second): fastest times especially seen in vasodilatory states (e.g. systemic inflammation, hyperthermia) – often accompanied by tachycardia and congestion.
    - CRT may also be fast in mild (early compensatory) hypovolaemic shock.



As mentioned above the most important questions to answer in a collapsed patient are:

- **Is systemic perfusion normal? Perfusion is a key concept in emergency medicine.**
- **Is there a murmur or gallop sound suggesting possible primary cardiac disease?**
- **Is there suspicion of a potentially clinically significant dysrhythmia?**

Additional notes on perfusion and dysrhythmias will be presented here and notes on primary cardiac disease and congestive heart failure are included later.

Shock and Systemic perfusion assessment

Shock

Shock essentially occurs when **systemic tissue oxygen delivery reaches a critically low level**. This may be due to:

- Systemic hypoperfusion
- Severe hypoxaemia
- Severely reduced oxygen-carrying capacity, typically due to severe anaemia

Inadequate oxygen delivery to cells means that they are unable to produce energy – there is a discrepancy between oxygen delivery and cellular oxygen demand. If the degree of shock is sufficiently severe or prolonged, irreversible cell damage can occur and treatment is invariably unsuccessful. **Systemic hypoperfusion** is the most common cause.

Systemic perfusion

Perfusion:

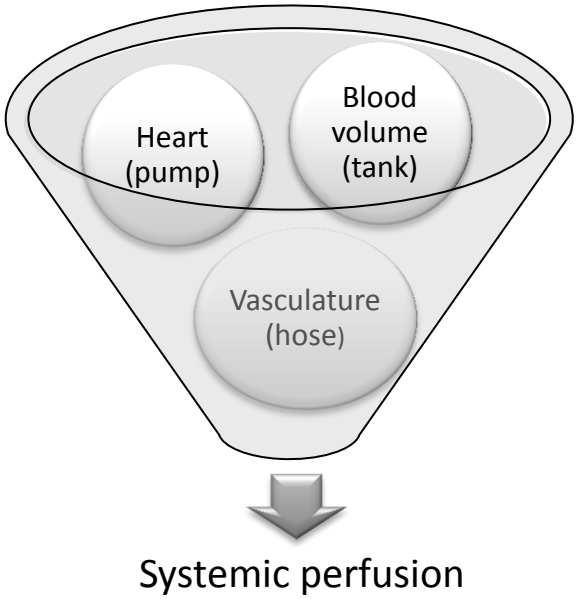
"the passage of a fluid through a specific organ or an area of the body." (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier)

"Bathing an organ or tissue with a fluid" (McGraw-Hill Concise Dictionary of Modern Medicine. © 2002 by The McGraw-Hill Companies, Inc)

What we are talking about here is assessing *systemic or generalised tissue/organ perfusion, i.e. the 'macrocirculation'.* In veterinary medicine, cardiovascular examination forms the mainstay of this assessment. There is much debate about the sensitivity and accuracy of physical examination parameters for assessing systemic perfusion and on-going research and investigation in human medicine into additional or indeed alternative and more sensitive parameters. One such parameter is blood lactate concentration which will also be discussed here. However physical examination is easy to perform and repeat and free of charge (after the initial fee!); it remains crucial in veterinary medicine. These notes will also mention systemic arterial blood pressure measurement and measuring urine output.

Systemic perfusion is essentially determined by three things and one or more of these may be abnormal in any individual patient:

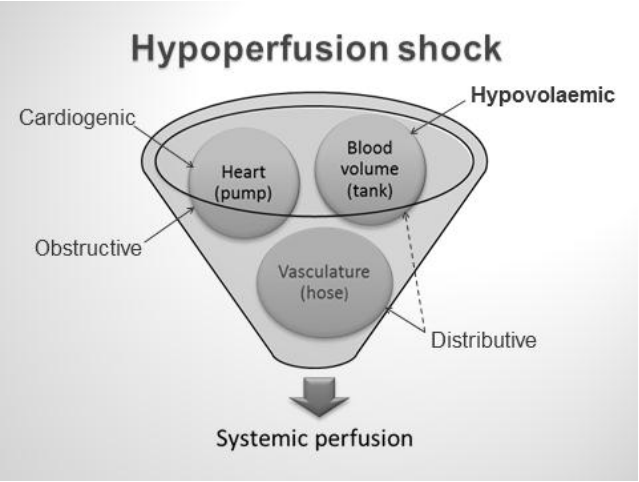
- The tank, i.e. intravascular fluid/blood volume
- The pump, i.e. how well is the heart able to pump blood.
- The hose: what is the size of the vascular space; are the perfusing vessels dilated or constricted? And is there a problem with flow through the container? Is flow obstructed in any way?

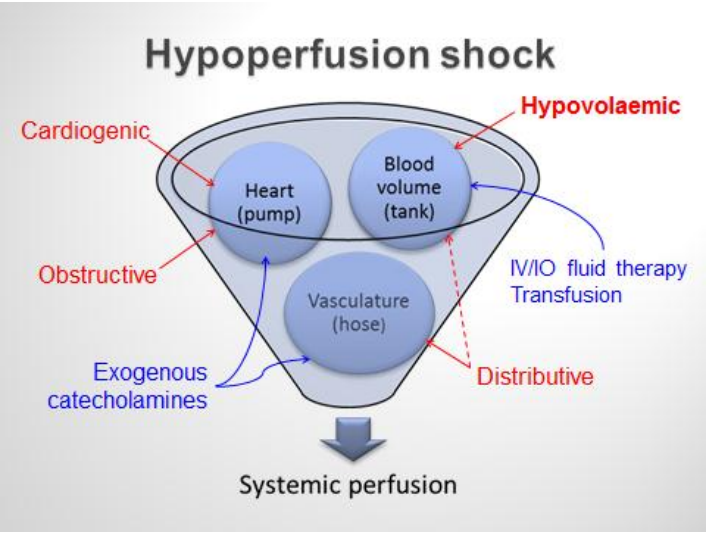


There are **four types of hypoperfusion-related shock** but clearly more than one type may be present in the same patient:

Hypovolaemic shock
Distributive shock
Cardiogenic shock
Obstructive shock

Remember that in any patient in shock from systemic hypoperfusion, there may be one or more of the four forms occurring concurrently. Various disorders can cause systemic hypoperfusion via different mechanisms that may affect the intravascular fluid volume, the size of the vascular container and/or the cardiac pump.





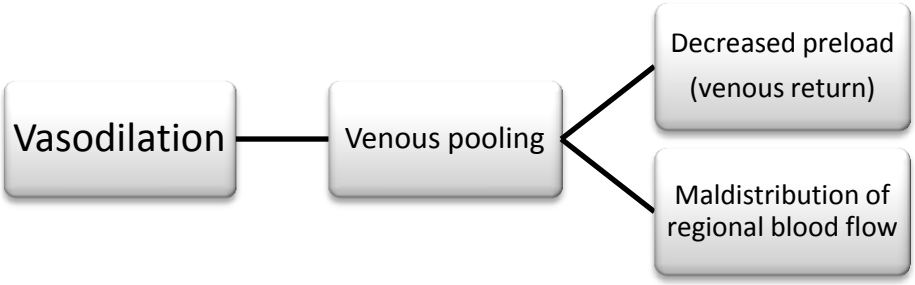
Hypovolaemic shock

Hypovolaemia = reduction in *effective circulating intravascular volume*
Effective circulating intravascular volume = that part of the extracellular fluid (ECF) within the vascular space that is 'perceived' by the body (i.e. by the relevant receptor mechanisms) as effectively perfusing tissues.
Most common cause of systemic hypoperfusion in dogs and cats; fluid loss is hypertonic or isotonic (tonicity is related to sodium concentration).
Fluid loss may affect just the intravascular space (e.g. early on in haemorrhage) or the extravascular space as well (e.g. salt and water loss, for example in vomiting and diarrhoea).

See more below

Distributive shock

Generalised inappropriate vasodilation (predominantly due to the vasomotor effects of inflammatory mediators) occurs so that the size of the vascular container is increased, sometimes quite spectacularly, i.e. there is abnormal vessel tone with decreased afterload. This means that even if no loss of intravascular fluid has occurred (i.e. there isn't an absolute hypovolaemia), systemic perfusion may be inadequate with a concurrent state of relative hypovolaemia and fluid being distributed in an abnormal way.



Assessment of perfusion parameters in distributive shock can be more challenging with sometimes less predictable changes. As with hypovolaemic shock, the treatment of distributive shock involves the use of aggressive intravenous crystalloid fluid therapy to 'fill the container'. Many of these patients have systemic vasculitis and there may therefore be a rationale to use a synthetic colloid early in these patients.

More severe cases can have spectacular vasodilation with minimal improvements in perfusion despite significant intravenous fluid resuscitation. The early use of vasopressors in patients with moderate-to-severe distributive shock may be rational to 'shrink the container'. Myocardial depression is thought to be a component of septic shock and an agent with a positive inotropic effect may be rational.

Causes:

- Systemic inflammatory response syndrome (SIRS)
    - Sepsis
    - Severe acute pancreatitis
    - Major tissue trauma
    - Neoplasia
    - Burn injury
- Anaphylaxis/anaphylactoid reaction
- 'Neurogenic' (spinal) shock

Dogs:

- Sepsis and severe acute pancreatitis are the two most common causes of distributive shock in dogs.

- Early on when intravascular volume remains adequate, dogs in distributive shock typically have a *hyperdynamic vasodilatory* cardiovascular picture, i.e. tachycardia, hyperdynamic pulses, markedly hyperaemic mucous membranes and a fast capillary refill time.
- With the onset of concurrent severe hypovolaemia, tachycardia progresses but pulses become weaker and CRT more prolonged. However, unlike dogs with uncomplicated severe hypovolaemia, dogs in *severe hypodynamic* distributive shock are likely to retain colour in their mucous membranes (due to lack of peripheral vasoconstriction) that may be normal in appearance or hyperaemic through to red.

Cats:

- Major tissue trauma is a relatively common cause of SIRS in cats and when this occurs as a result of bite wounds, sepsis may also be present.
- As with hypovolaemia, and unlike dogs, cats in distributive shock are more likely to present with a hypodynamic cardiovascular picture that is typical of hypovolaemic shock in this species

Cardiogenic shock

When presented with a patient in shock it is tempting to start aggressive intravenous fluid therapy in all cases. However such therapy may clearly be disastrous in patients with cardiogenic shock and so it is important to always be alert to findings – signalment, historical and clinical – that may implicate cardiac dysfunction as the cause of the shock and to respond appropriately in terms of fluid use.

Primary systolic or diastolic cardiac dysfunction results in an inability of the heart to pump blood adequately with reduced cardiac output (forward failure) and consequent haemodynamic abnormalities that may include systemic hypoperfusion (cardiogenic shock). Cardiogenic shock is essentially an extreme manifestation of forward heart failure with pump malfunction.

Causes of cardiogenic shock included cardiomyopathy, valvular disease, and severe tachy- or bradydysrhythmias. Depending on the underlying cause, treatment of cardiogenic shock may include diuresis for congestive heart failure, anti-dysrhythmic therapy and potentially use of a positive inotrope. All patients will likely benefit from supplemental oxygen and minimal stress is essential.

Obstructive shock

Obstructive shock is the result of obstruction of arterial blood flow from the heart or of venous return to the heart. The most common example of this in small animals is pericardial tamponade. Other causes include severe pneumothorax, constrictive pericarditis and pulmonary thromboembolism (PTE). Depending on the cause some of these patients may benefit from judicious fluid therapy but care is needed and cardiovascular status may not improve unless the obstruction can be relieved.

Systemic perfusion assessment

Cardiovascular examination – always the priority!

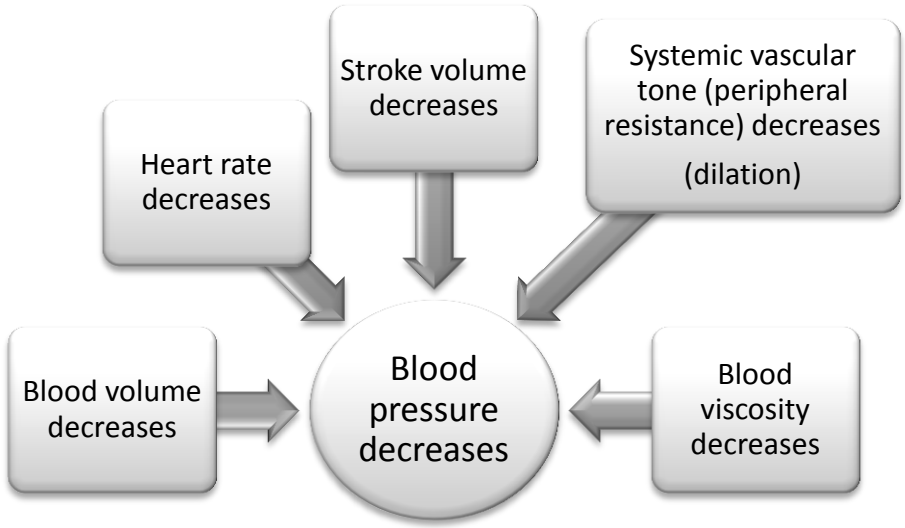
- Plus subjective cardiac contractility on emergency ultrasound

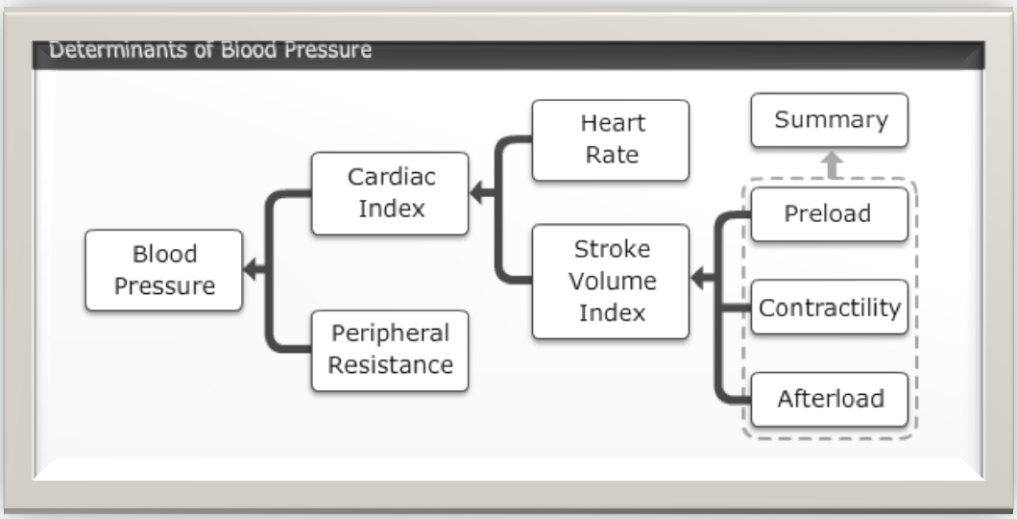
Arterial blood pressure
Blood lactate concentration
Urine output

Systemic arterial blood pressure

Measurable hypotension can be a late event in hypovolaemia so a patient may be in shock with reduced organ perfusion despite normal arterial blood pressure.

Systemic arterial blood pressure depends on a number of factors.





(Preload = volume of blood in ventricle; Contractility = force of contraction applied; Afterload = resistance to contraction)

Normal arterial blood pressure (mmHg)	Adult dog	Adult cat
Mean	60-100	60-100
Systolic	90-140	80-140
Diastolic	50-80	55-75

Mean arterial pressure (MAP) is most important.
There is no direct correlation between systolic or diastolic pressure and MAP.
Peripheral indirect blood pressure measurement may be less accurate in:

- Very small animals
- Hypotension
- Dysrhythmias
- Peripheral oedema
- Vasoconstriction

Doppler ultrasonography measures systolic blood pressure; this technique may be the most reliable indirect method in animals under 10 kg or those with hypotension or dysrhythmias.
There is some suggestion that the Doppler technique may underestimate systolic blood pressure by 10-15 mmHg in cats and more closely approximate MAP; however this was in one single study of anaesthetised healthy cats so caution is needed in interpretation.
One shortcoming of using Doppler ultrasonography is the inability to measure diastolic blood pressure; the significance and importance of diastolic hypotension is something that so far has received little attention but is likely to in the future.

Oscillometric sphygmomanometry devices usually measure MAP and then use this to calculate systolic and diastolic pressures via algorithms; MAP may therefore be most reliable. Newer devices may be more reliable in general in cats and smaller dogs than older devices were.

The recommended guideline for indirect BP measurement is that the width of the cuff should be 30-40% of the circumference of the leg at the site of the artery being used. Too small a cuff will likely yield a falsely high pressure; too large a cuff, a falsely low pressure.

Basic approach to hypotension

Address the underlying cause if possible. Causes include:

- Decreased cardiac output due to reduced circulating volume (hypovolaemic shock) or blood flow obstruction (obstructive shock)
- Myocardial failure (cardiogenic shock)
- Severe tachydysrhythmia or bradydysrhythmia (cardiogenic shock)
- Decreased systemic vascular resistance due to peripheral vasodilation, e.g. sepsis (distributive shock)

Administer aggressive intravenous fluid therapy tailored to resuscitation end-points (typically physical examination parameters, blood pressure, lactate) – contraindicated for cardiogenic causes.
Consider early use of vasopressor/inotrope, especially in distributive shock. Reliable blood pressure monitoring is preferred when using vasopressors or inotropes.

Blood lactate measurement

Basic lactate physiology

Lactate production is a protective response by the body to allow cellular energy production to continue when tissue oxygen supply is inadequate for aerobic metabolism.
When lactate production exceeds lactate clearance (mostly by the liver and to a lesser extent the kidneys), plasma lactate rises (hyperlactataemia).
Hyperlactataemia is a marker of the severity of tissue hypoxia. It is not always associated with acidaemia or indeed abnormal base deficit depending on buffer reserves and other existing acid/base disturbances.
In normal dogs, arterial and venous, both jugular and cephalic, lactate concentrations are very similar and differences are not clinically significant.

Causes of hyperlactataemia

Two important points about lactate to bear in mind are:
1) Not every patient will show the same degree of hyperlactataemia for the same severity of systemic hypoperfusion and in fact in a small proportion of patients despite reduced tissue oxygen delivery lactate does not seem to rise.
2) There are some patients that have so-called 'cryptic' shock where hyperlactataemia is present due to reduced tissue oxygen delivery and yet haemodynamic parameters including blood pressure are normal (normotensive shock), i.e. based on our usual assessment the patient does not appear to be in shock.

Clinical aspects of hyperlactataemia

Single lactate measurements should not be used prognostically but serial measurements have a role. It is more valid to monitor whether lactate normalises or not with therapy which will be affected by the severity of the underlying problem and how well it can be controlled (e.g. blood loss versus sepsis).

Moderate-to-severe hyperlactataemia is typically due to systemic hypoperfusion or muscle activity (seizures, exercise).

Systemic hypoperfusion is the most common cause of hyperlactataemia (Type A) and lactate is most often used as an objective marker of the severity of shock:

- Plasma lactate tends to increase in proportion to the severity of the hypoperfusion; but it is essential to realise that this does not reflect reversibility.

- In hypoperfused patients without an additional on-going cause of hyperlactataemia (e.g. sepsis, neoplasia), hyperlactataemia should resolve relatively quickly (minutes to a few hours) with successful fluid therapy offering a comparatively real-time marker of improving perfusion status.

- In some patients plasma lactate appears to increase initially when aggressive fluid therapy is started before then trending downwards. This is thought to be because improved perfusion to anaerobic tissues allows accumulated lactate to be collected by the circulation; this is then cleared by the liver and kidneys.

Type A hyperlactataemia (Due to tissue hypoxia)	Absolute oxygen deficiency	Generalised systemic hypoperfusion (Shock) MOST COMMON CAUSE	Hypovolaemic Distributive Cardiogenic Obstructive
		Local hypoperfusion	Aortic (and other) thromboembolism Splanchnic ischaemia, especially with gastrointestinal necrosis
		Severe hypoxaemia	E.g. P_aO_2 less than 30-40 mmHg
		Severe anaemia without hypoperfusion	Typically PCV less than 10-15 %
	Relative oxygen deficiency (energy requirements greater than aerobic metabolism can provide)	Increased glycolysis: Hyperlactataemia typically resolves quickly in these cases	Extreme muscle activity (e.g. seizures, trembling/tremors) Strenuous exercise
Type B hyperlactatemia (No clinical evidence of tissue hypoxia) For some/many of these causes the mechanism(s) for plasma lactate increase remains to be clarified.		Underlying diseases	Sepsis* Severe liver disease with insufficiency Neoplasia (especially lymphoma) Diabetes mellitus Phaeochromocytoma Thiamine deficiency

Furthermore it may be that in some cases occult hypoperfusion exists but cannot be detected. *Hyperlactataemia in sepsis is likely multifactorial, especially from hypoperfusion, hypermetabolism and possibly abnormal lactate metabolism. *(Based on Hughes, D. Lactate: What Does It Really Tell Us? IVECCS Proceedings 2010)*	Many different drugs and toxins, e.g.	Paracetamol (acetaminophen) Cyanide Adrenaline (Epinephrine) Ethanol Ethylene glycol Glucose Insulin Morphine Nitroprusside Propylene glycol (e.g., in activated charcoal) Salicylates Terbutaline
	Congenital metabolic defects	Mitochondrial myopathy Defects in gluconeogenesis
	Miscellaneous	Alkalosis/hyperventilation Hypoglycaemia

In the early stages of hypoperfusion when compensatory mechanisms are adequate, hyperlactataemia may well not be present. The onset of hyperlactataemia typically suggests decompensation (with tissue oxygen deficiency) and should always therefore be considered a serious finding.

Plasma lactate may rise during blood sampling if significant or prolonged restraint is required or prolonged venous occlusion occurs; such hyperlactataemia is typically only mild. However more marked hyperlactataemia may occur if there is trembling or other muscle activity during restraint, especially in cats.

Urine output

'Normal' urine output must be interpreted in the context of each individual patient and a range of **0.5-2 ml/kg/hour** is typical. Normal urine production requires adequate renal perfusion, fluid balance and kidney function. An intact urinary tract is then necessary for normal external urine voiding.

The kidneys receive a significant percentage of the cardiac output and renal vasoconstriction and decreased urine output is an appropriate response to hypovolaemia. Reduced urine production (oliguria) and increased urine specific gravity (hypersthenuria) are suggestive of fluid deficit and the need for more rapid infusion. Therefore normalisation of urine output may be a useful end-point of fluid resuscitation.

Placement of an in-dwelling urinary catheter attached to a closed collection system is reasonably easy to achieve in most cases. However placement of an in-dwelling urethral catheter is not considered a routine part of fluid resuscitation and the associated discomfort and risks of hospital-acquired infection must be borne in mind. Urine output monitoring definitely has a role in a proportion of cases (e.g. very sick animals, post-operative cases).

Although not ideal, if an in-dwelling urinary catheter cannot be used, it is possible to estimate urine output using pre-weighed incontinence pads. The patient is only allowed to urinate on incontinence pads which are then weighed; each 1 g increase in weight is approximately equal to 1 ml of urine production.

Hypovolaemia

It is essential to prioritise perfusion assessment and intravascular volume status over hydration concerns.

Hypovolaemia and dehydration are not the same although both are treated with fluid therapy. Hypovolaemia is the most common cause of abnormal perfusion and shock in dogs and cats and can be fatal. A basic understanding of body fluid distribution is essential to appreciate the concepts of perfusion, intravascular volume status, shock and dehydration.

Body fluid compartments

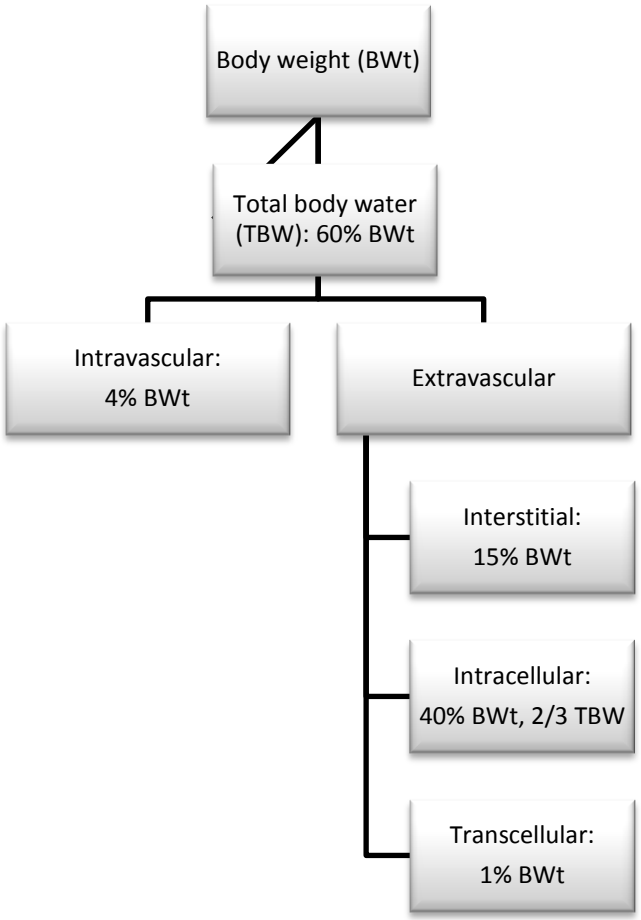
The intravascular fluid compartment is considerably smaller than the extravascular compartment and yet normal intravascular volume status is essential as it is responsible for tissue perfusion.

Hypovolaemia is essentially an intravascular volume deficit whereas dehydration predominantly affects the extravascular compartment.

Fluid (water and solutes) continually shifts between compartments under the influence of osmotic concentration gradients and oncotic and hydrostatic pressure gradients (Starling's forces).

In normal animals physiological water losses (through the urinary, respiratory and cutaneous routes) are well compensated by fluid movement between compartments.

Abnormal fluid losses may be iso-, hypo- or hypertonic and their effects depend on both their magnitude and what changes occur in extracellular fluid osmolarity.



Hypovolaemia

Hypovolaemia = reduction in *effective circulating intravascular volume*
Effective circulating intravascular volume = that part of the extracellular fluid (ECF) within the vascular space that is 'perceived' by the body (i.e. by the relevant receptor mechanisms) as effectively perfusing tissues.
Most common cause of systemic hypoperfusion in dogs and cats; fluid loss is hypertonic or isotonic (tonicity is related to sodium concentration).
Fluid loss may affect just the intravascular space (e.g. early on in haemorrhage) or the extravascular space as well (e.g. salt and water loss, for example in vomiting and diarrhoea).

Causes of hypovolaemia

Most common:

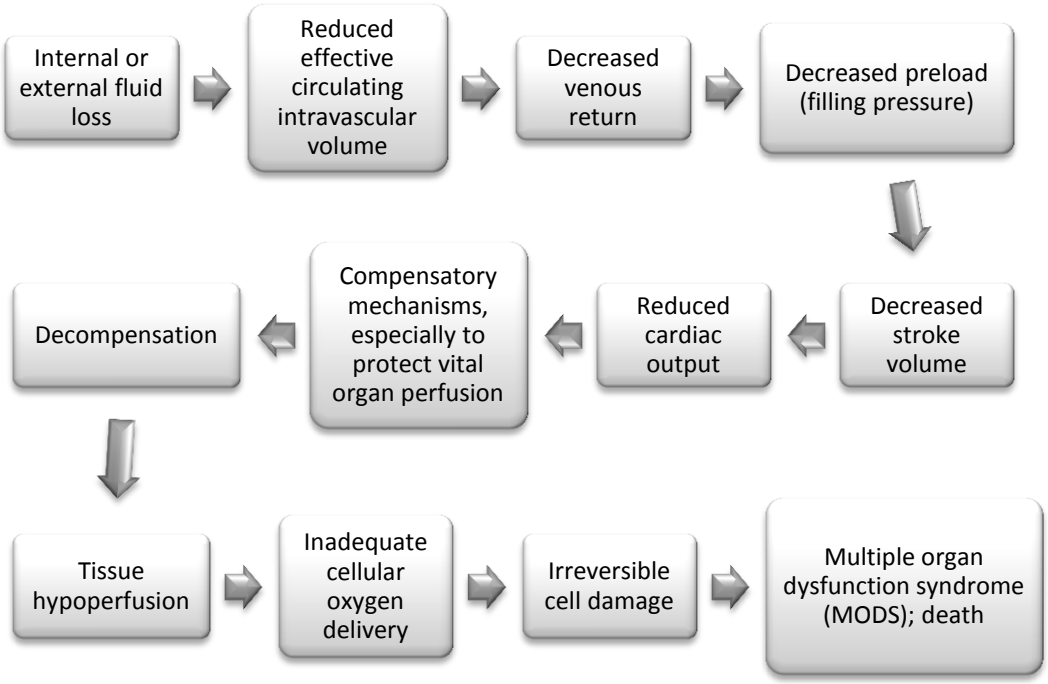
- Haemorrhage:
    - Trauma, coagulopathy, ruptured tumour
- Vomiting and diarrhoea
- Severe dehydration

Less common:

- Third-space fluid loss:
  - Gastrointestinal tract*
  - Peritoneal, pleural or interstitial space
- Burn injury (hypovolaemia is common but burn injury is relatively uncommon in dogs and cats)
- Severe polyuria
- Neoplasia

*The gastrointestinal tract is a large space into which considerable fluid loss may occur, for example in patients with severe gastroenteritis.

Pathophysiology of hypovolaemia



"Shock breeds shock": in shock the tissues of the cardiovascular system also become under perfused which compromises their function reducing their ability to compensate for the shock state, i.e. a vicious circle ensues.

Compensatory mechanisms:

The three main compensatory responses to hypovolaemia in a timeframe of minutes are:

- Increase in heart rate (positive chronotropy)
- Increase in cardiac contractility (positive inotropy)
- Vasoconstriction

These are sympathetic nervous system driven.

Ideally patients will be identified when in the compensatory stage of shock and aggressive intervention started. The prognosis is certainly not hopeless once the patient has started to decompensate (i.e. the physiological reserve is overwhelmed) but decompensation may herald a rapid deterioration into the irreversible stage. Unfortunately some patients do not present until they are already in late decompensation or in an irreversible state of shock – although this may be highly suspected at the time of presentation, there isn't a definitive way of knowing this at the outset.

The hypovolaemic dog

In dogs with 'uncomplicated' hypovolaemia physical examination perfusion parameters tend to change in a predictable way both as hypovolaemia progresses and as normovolaemia is restored.

Perfusion parameter	Mild hypovolaemia Compensatory	Moderate hypovolaemia Early decompensatory	Severe hypovolaemia Late decompensatory
Heart rate	120-150 bpm	150-170 bpm	170-220 bpm
Femoral pulse	Bounding, snappy	Weak	Very weak or thready
Dorsal pedal pulse	Readily palpable	Just palpable	Not palpable
Mucous membrane colour	Normal, pinker	Pale pink	Very pale/white
Capillary refill time	≤ 1 second	1-2 seconds	> 2 seconds or not detectable
Mentation	Usually normal	Depressed	Severely depressed
Extremities	Usually normal	Cool (or normal)	Cold

Compensatory phase/mild hypovolaemia:

- Sympathetic nervous system activation
- Increase in heart rate and cardiac contractility
- Peripheral vasoconstriction
- Hyperdynamic clinical picture

Early decompensatory phase/moderate hypovolaemia:

- Progressive failure of compensatory mechanisms results in reduced tissue perfusion

Late decompensatory phase/severe hypovolaemia:

- Systemic perfusion is severely compromised; hypodynamic clinical picture
- Usually tachycardic but some dogs may have an inappropriately 'normal' or slow heart rate – this is due to failure to sustain the compensatory chronotropic response

Note that physiological sinus tachycardia is unlikely to exceed 220-240 bpm in a dog (300 bpm in a cat). Faster heart rates are likely to be due to tachydysrhythmia.

The hypovolaemic cat

Given that the typical hypovolaemic cat has a hypodynamic clinical picture, a cat presenting like this should be seen as having a life-threatening problem but the prognosis is not necessarily grave if appropriate treatment is provided.

'Cats are not small dogs' and the classic presentation for the hypoperfused cat is a hypodynamic picture with a hyperdynamic picture (tachycardia, hyperaemic membranes, fast CRT) being rarely identified.

Typical hypovolaemic cat:

- 'Inappropriate' bradycardia – heart rate 120-160 bpm
- Weak or absent pulses
- Pale mucous membranes
- Prolonged (> 2.5 seconds) or undetectable CRT
- Depression
- Hypothermia

The reason why cats tend to present with this clinical picture most often remains unclear. In particular the tendency towards bradycardia is unexplained but may well represent a difference in sympathetic-parasympathetic balance between cats and dogs or a greater degree of autonomic dysfunction in cats. Or potentially a relative dominance in cats of a cardiovascular reflex known as the Bezold-Jarisch reflex may be involved but this is just conjecture.

[There remains much to be unravelled about the BJR but its physiological roles may include blood pressure regulation, homeostatic response to hypovolaemia, and effector of haemodynamic changes during myocardial ischaemia. Stimulation of cardiac inhibitory receptors (by currently unknown stimuli) may trigger the reflex causing bradycardia and peripheral vasodilation with consequent hypotension. This reflex has been studied experimentally in cats with artificial stimulation of the reflex but its role in non-experimental cats remains entirely unclear.]

Should hypothermic hypovolaemic cats be warmed aggressively?

Hypothermia significantly decreases the cardiovascular response to fluid resuscitation. However it is possible that re-warming the patient too quickly before administering sufficient fluid therapy may worsen their perfusion status as the increase in body temperature may cause peripheral vasodilatation thereby increasing the intravascular space. Not everyone agrees with this – some people believe that non-sweating animals like dogs and cats do not vasodilate (significantly) with warming especially when core temperature is low and there is even some suggestion that cats in shock may already be relatively vasodilated peripherally compared to dogs. These individuals therefore argue for more aggressive warming early on.

However the most widely accepted recommendation is to limit on-going heat loss with passive warming (e.g. wrap in blankets, place in incubator) during initial fluid resuscitation. In many cases as the patient's perfusion improves their rectal temperature will often increase notably; however more aggressive warming can be performed following initial fluid resuscitation if still thought necessary.

'Complicated' hypovolaemia

Hypovolaemia is not always 'uncomplicated'. A proportion of hypovolaemic patients have other abnormalities that may affect one or more of the physical perfusion parameters described. Common examples include:

- Mucous membranes may remain pale despite appropriate fluid therapy in an animal with severe anaemia
- Mentation may remain depressed in an animal with head trauma despite appropriate fluid therapy as a result of raised intracranial pressure
- Dogs suffering an Addisonian crisis may be inappropriately bradycardic despite poor perfusion for a variety of reasons of which one is hyperkalaemia
- Animals with urethral obstruction or urinary tract rupture may be inappropriately bradycardic due to hyperkalaemia

Dehydration

For clinical purposes, dehydration is water **and solute loss in excess of intake.**
Excess loss in disease states may occur via the:

- Gastrointestinal tract: most common route in small animals, especially with diseases that cause vomiting and diarrhoea
- Urinary tract with polyuria (e.g. chronic renal failure)
- Less common routes include the respiratory system (excessive panting), the skin (i.e. burns), and third-spacing (ascites, peritonitis, pleural effusion).

Excess fluid loss in disease states is usually associated with a decrease in water intake (anorexia).
Fluid loss is hypotonic or isotonic (tonicity is related to sodium concentration).

Fluid loss in dehydration is mainly from the extravascular compartment. The effect on intravascular volume depends on both the degree of fluid loss and the tonicity (isotonic or hypotonic) of the fluid.

Hydration assessment

History

The history can provide an indication of potential fluid deficits. The most important information includes:

- Food and water consumption
- Gastrointestinal losses, i.e. vomiting and diarrhoea: number of episodes and approximate quantities
- Urinary losses: frequency and volume of urination

If the history is suggestive of fluid and electrolyte loss in excess of intake, then the patient should already be considered to be 5% dehydrated.

Physical examination

Physical examination hydration parameters are related to interstitial volume. They are:

- Moistness of mucous membranes
- Skin turgor (elasticity)
- Presence and degree of globe retraction (sunken eyes)

Perfusion parameters become relevant if dehydration is severe enough to cause hypovolaemia.

There a number of different versions of the table below that are used to approximate dehydration on the basis of physical examination.

Severity of dehydration (estimated % of body weight)	**Progression of physical examination findings**
<5% (NONE)	Normal Assume dehydration based on history
SOME: • Mild (5-6%)	Skin turgor mildly reduced
• Moderate (6-10%)	Skin turgor progressively reduced Mucous membranes dry Eyes sunken
SEVERE (10-15%)	Complete loss of skin turgor Mucous membranes very dry Eyes severely sunken and dull Progressive signs of hypovolaemia, ultimately leading to shock and death

These guidelines only provide a crude estimation of fluid loss in the dehydrated patient. There are a number of potential inaccuracies that must be borne in mind. For example, skin turgor can be affected by the degree of subcutaneous fat present (with obese animals having increased turgor), and mucous membrane moistness can be affected by salivation (e.g. due to nausea). Moreover these sorts of findings are likely to have quite high variability between individual clinicians – i.e. two people assessing the same patient may well come up with a different severity of dehydration if specific percentages are required; hence broader categories of dehydration severity are most rational. In the context of dehydration, it is probably better to under- rather than overestimate severity.

Short-term changes in body weight reflect changes in fluid balance rather than nutritional status

Clinical pathology

All of the following may increase with dehydration:

- Packed cell volume (PCV) and serum total solids (TS)
- Blood albumin (and globulin) concentration
- Blood urea and creatinine concentrations (pre-renal azotaemia is typically mild) and urine specific gravity

Urine specific gravity in dehydration:

Ideally azotaemia should be interpreted alongside a concurrent urine specific gravity (USG). Ideally USG should be determined prior to fluid therapy; however it is essential not to delay fluid therapy unnecessarily for the sole purpose of obtaining a urine sample.

In a dehydrated patient USG prior to fluid therapy should be increased as the kidneys will try to compensate for the fluid loss; this is achieved by enhancing water and sodium reabsorption in the distal part of the renal tubules under the influence of antidiuretic hormone (ADH) and the mineralocorticoid aldosterone.

In some diseases the kidneys are unable to concentrate the urine despite the presence of dehydration due to abnormalities in the renal medullary concentrating gradients (renal medullary washout).

PARENTERAL FLUID THERAPY

While parenteral fluid therapy can be life-saving, especially in non-cardiogenic shock, as with most drugs it also has the potential to cause harm. Inadequate fluid administration is clearly a concern but remember that over-zealous administration can also be harmful for example causing tissue interstitial oedema, pulmonary oedema being one main concern, and possible dilutional coagulopathy.

Types of Parenteral Fluids

Crystalloids

Crystalloids are electrolyte solutions that can pass freely out of the bloodstream through the capillary membrane.

Crystalloid solution	Na^+	K^+	Cl^-	Ca^{2+}	Osmolality (mOsm/L)
REPLACEMENT:					
Hartmann's (buffered LRS)	131	5	111	2	272
Lactated Ringers solution	130	4	109	1.5	273
0.9% NaCl ('normal' saline)	154	0	154	0	308
Normosol-R	140	5	98	0	295
Plasmalyte 148	140	5	98	0	295
MAINTENANCE:					
0.45% NaCl + 2.5% dextrose (glucose) [requires additional potassium]	77	0	77	0	203
Normosol-M + 5% dextrose	40	13	40	0	363
Plasmalyte M + 5% dextrose	40	16	40	2.5	377
Plasmalyte 56 + 5% dextrose	40	13	40	0	363
OTHERS:					
0.45% NaCl ('half strength' saline)	77	0	77	0	154
0.9% NaCl + 5% glucose	154	0	154	0	560
0.18% NaCl + 4% glucose	30	0	30	0	
7.2% NaCl (hypertonic saline)	1232	0	1232	0	~2450
5% dextrose in water (D5W) [equivalent to 100% free water)	0	0	0	0	252

Electrolyte concentrations in *mmol/L*

They are classified as *isotonic, hypertonic* or *hypotonic* based on how their tonicity compares to that of extracellular fluid; the tonicity is related to the sodium concentration and it is the tonicity (plus effects on hydrostatic and oncotic pressure, i.e. Starling's forces) that determines how the crystalloid solution is distributed between fluid compartments following administration into the bloodstream.

Isotonic crystalloids

Replacement isotonic crystalloids

Their tonicity and electrolyte composition are similar to that of extracellular fluid. They are an appropriate first choice in the vast majority of cases and are used in two main ways:

- At high rates to treat hypovolaemia either alone or in combination with other fluid types (colloid, hypertonic saline)
- At low rates to replenish fluid deficits in dehydrated patients

The two most commonly used replacement crystalloid solutions are buffered lactated Ringers solution (LRS, Hartmann's solution, compound sodium lactate) and 0.9% sodium chloride (normal strength or physiological saline). They are both typically classified as isotonic although in reality LRS is slightly hypotonic compared to mammalian extracellular fluid.

Following intravascular administration, these fluids equilibrate relatively quickly with the interstitial space and 75-85% of the administered volume is likely to have left the bloodstream 30-60 minutes after infusion. This is why large volumes are required to effectively expand the intravascular compartment in hypovolaemia and is also the reason that these solutions are used to replenish extravascular fluid losses in dehydration.

0.9% sodium chloride vs. buffered lactated Ringers solution – does it matter which one I use?

The composition of these fluids is not the same and the following is noteworthy:

- LRS contains a small amount of calcium and potassium so 0.9% NaCl is usually used in hypercalcaemia and hyperkalaemia
- LRS contains a source of bicarbonate (lactate) and is therefore considered to be alkalinising; 0.9% NaCl does not contain a source of bicarbonate and may contribute to acidaemia via a hyperchloraemic metabolic acidosis – it may therefore be less desirable in acidaemic patients.

While it is worth bearing the above considerations in mind when choosing which fluid to use, in reality in most cases, it makes no clinically significant difference which one is used – the emphasis being on 'no clinically significant difference'. It is definitely more important to make sure that a patient in need of fluid resuscitation receives one or other of these solutions rather than worrying about more theoretical concerns or reported contraindications.

LRS contains a small amount of calcium which can bind to the citrated anticoagulant in blood products. This can inactivate the anticoagulant and promote the formation of clots in the donor product. LRS should not therefore be mixed with blood products.

For some more discussion on this subject in the context of tomcat urethral obstruction check out this podcast episode: http://www.veteccsmalltalk.com/episode/4

Maintenance isotonic crystalloids

Commercial maintenance crystalloid solutions are more-or-less isotonic and have an electrolyte composition that is more similar to insensible electrolyte losses in healthy animals. There is therefore an argument for using these solutions in animals requiring maintenance fluid therapy only, i.e. once hypovolaemia and dehydration have been corrected.

However the potassium content of maintenance fluids is relatively high and they are therefore limited to slow infusion rates. Furthermore the majority of hospitalised patients are not 'healthy' and have on-going electrolyte losses and reduced enteral intake. Maintenance crystalloid solutions are therefore very infrequently indicated for sole use in veterinary medicine; some hospitals routinely keep hospitalised patients on maintenance fluids at a maintenance rate, and then use additional replacement fluids to meet additional requirements.

Replacement isotonic crystalloid solutions can be used, and frequently are, for continued fluid therapy in hospitalised patients. However it is important to be aware that:

- These solutions typically contain little or no potassium – therefore hypokalaemia may develop in animals with reduced potassium intake and supplementation may be required.
- These solutions have a relatively high sodium content that can lead to mild hypernatraemia – this is rarely clinically significant but noteworthy nonetheless.

Hypertonic saline

E.g. 3% or 7.2%-7.5% sodium chloride solution
Causes intravascular volume expansion by drawing water in from the extravascular space down an osmotic gradient. Although transient, a rapid intravascular volume expansion is seen (typically within 5 minutes) – in dogs the haemodynamic effect is comparable to a 60-90 mL/kg bolus of replacement crystalloid.

Recommended doses (over 5 minutes): Dogs: 4-7 mL/kg IV
Cats: 2-4 mL/kg IV

Indications:

Volume resuscitation: especially large/giant breed dogs where it may not be possible to administer isotonic crystalloids fast enough

- Commercial preparations including hypertonic saline and synthetic colloid (e.g. hypertonic saline with dextrans) are available; the inclusion of a colloid prolongs intravascular volume expansion.

Intracranial hypertension: hypertonic saline causes fluid to shift from the brain parenchyma into the circulation

- Hypertonic saline is especially useful in head trauma patients that are also hypovolaemic as it addresses both the hypovolaemia and the possible raised intracranial pressure.

The effect of hypertonic saline administration usually lasts for up to 30 minutes and is associated with osmotic diuresis and rapid sodium distribution. It must be followed by the use of a replacement isotonic crystalloid or colloid.

Contraindications:

Concurrent dehydration (these patients already have a deficit in their extravascular compartment which will be worsened by hypertonic saline use)
Heart failure or cardiogenic shock (due to the risk associated with a rapid and sizeable surge in intravascular volume and preload)
Active haemorrhage, especially pulmonary contusions
Oliguric renal failure

Transient hypernatraemia and hyperchloraemia are likely.

Hypotonic saline

Probably the only ready-made hypotonic saline solution that has a clinic use in small animals is 0.45% 'half strength' sodium chloride solution.

- This is used most commonly together with other solutions in the gradual correction of sodium abnormalities.
- It is also used occasionally at a low rate to replace fluid deficits while limiting the sodium challenge in dehydrated animals with heart disease.
- This solution is 50% free water

Hypotonic fluids should never be used in the resuscitation of hypovolaemia as the decreased sodium content of these fluids causes them to stay in the intravascular space for an even shorter period of time; they are therefore an inefficient resuscitation fluid. Furthermore when administered in large quantities hypotonic fluids can cause severe electrolytes abnormalities (especially severe hyponatraemia).

Synthetic colloids

Replacement crystalloid or synthetic colloid for reperfusion? Opinions vary here to an extent but replacement isotonic crystalloids are widely used as the first fluid of choice in virtually all patients. A synthetic colloid may be indicated early in certain populations ('capillary leak' syndrome; hypoproteinaemia) and in hypovolaemic patients showing poor response to crystalloids. But remember that commercial synthetic colloid preparations are typically colloid molecules in an isotonic crystalloid solution so you are still giving crystalloid when using a synthetic colloid. Remember also that synthetic colloids may have adverse effects and their safety in critical illness in particular remains to be clarified.

Colloid solutions consist of large molecular weight molecules that do not readily leave the bloodstream and therefore increase the colloid osmotic (oncotic) pressure of the plasma. Colloid molecules generally remain in the bloodstream for up to several hours. This draws fluid into and holds fluid in the vasculature causing plasma volume expansion. The volume and duration of plasma expansion that follows colloid administration depends in part on the specific colloid used – especially the size

(molecular weight) – as well as the dose given and the species in question; other individual patient-related factors are also important.

Proprietary synthetic colloid solutions are often made up to a colloid concentration of 6% or 10% in 0.9% sodium chloride or buffered LRS (Hartmann's). Non-synthetic (natural) colloid solutions that are currently used therapeutically include plasma and albumin solutions.

The three types of synthetic colloid solutions in veterinary use currently are hydroxyethyl starches (HES; a variety of products with a wide range of molecular weights, e.g. tetrastarch, pentastarch, hetastarch), gelatins and dextrans.

In general HES solutions cause longer plasma volume expansion and are excreted more slowly than other synthetic colloids; they are therefore considered more clinically useful.

- High molecular weight solutions have the longest duration of effect but are also associated with the greatest side effects.
- High molecular weight solutions are most likely to cause multifactorial dose-dependent coagulopathy; tetrastarch is considered the safest in this respect.
- Allergic reactions occur very infrequently with HES use but they have been reported.

In 2013 there was a worldwide recall of HES products due to concerns in human medicine over a possible increase in the need for renal replacement therapy and possible mortality associated with these fluids. Since then the debate and discussion has raged on. At the time of writing synthetic colloids – essentially hydroxyethyl starch – is not recommended as a minimum in people with critical illness, sepsis or burn injuries, but some clinicians avoid their use entirely and this may not be an unreasonable position in veterinary medicine either at this time. Furthermore the following paper was published in early 2016 (remember not take the abstract and conclusions at face value, ideally access the paper and critique it yourself!):

Hayes G, Benedicenti L, Mathews K. Retrospective cohort study on the incidence of acute kidney injury and death following hydroxyethyl starch (HES 10% 250/0.5/5:1) administration in dogs (2007–2010). J Vet Emerg Crit Care 2016. 26(1):35-40.

[ABSTRACT

Objective
To determine the incidence of in-hospital adverse outcomes including acute kidney injury (AKI) and death in a population of dogs admitted to the intensive care unit (ICU) receiving 10% hydroxyethyl starch (HES) [250/0.5/5:1] compared with the general ICU population, while controlling for illness severity.

Design
Cohort study conducted between January 2007 and March 2010.

Setting
Veterinary teaching hospital.

Animals
Consecutive sample of dogs receiving HES (*n* = 180) were compared with a randomly selected sample of dogs (*n* = 242) admitted to the ICU over the same period.

Interventions
None

Measurements and Main Results
AKI was defined as an at least 2-fold increase in baseline creatinine concentration or new onset of oliguria/anuria persisting for ≥12 hours. The primary outcome was a composite of in-hospital death or AKI. Unadjusted and adjusted analysis controlling for illness severity using the acute patient physiologic and laboratory evaluation ($APPLE_{fast}$) score and other confounders was performed. HES was administered either as incremental boluses (median dose 8.2 mL/kg/day, interquartile range [IQR] 5.0–11.3 mL/kg/day) or as a continuous rate infusion (CRI; median dose 26mL/kg/day, IQR 24.0–48 mL/kg/day). In unadjusted analysis, HES administration was associated with increased risk of mortality (odds ratio [OR] = 2.33, 95% confidence interval [CI] = 1.51–3.58, $P < 0.001$) or AKI (OR = 3.87, 95% CI = 1.21–12.37, $P = 0.02$). In an adjusted analysis after controlling for illness severity, admission type, and concurrent administration of blood products, HES administration remained an independent risk factor for the composite adverse outcome (OR = 1.98, 95% CI = 1.22–3.22, $P = 0.005$), with a number needed to harm (NNH) = 6 (95% CI = 4–23).

Conclusions
HES therapy is associated with increased risk of an adverse outcome including death or AKI in dogs. A randomized controlled trial investigating the safety of HES therapy in canine patients is warranted.]

At the time of writing Gelofusine® and Haemaccel® are the only synthetic colloids licensed for veterinary use. Both are gelatins and they have very similar properties. The molecules in these solutions are smaller than in other synthetic colloids and in general they cause the shortest duration of plasma volume expansion and are excreted most quickly from the body. Despite being unlicensed, other synthetic colloids are therefore typically preferred due to greater perceived efficacy. Dextrans are solutions of glucose polymers which are commercially available in the United Kingdom although more commonly used in the United States of America. They contain larger molecules than the gelatins and are therefore generally associated with a slightly longer duration of action and slower excretion from the body.

The most significant side effect associated with synthetic colloids, at least in the past, was their potential to cause multifactorial dose-dependent clotting abnormalities. Colloids also have a greater potential to cause intravascular overload and allergic reactions have been reported rarely.

- Gelatins are the colloid reportedly most likely to induce an allergic reaction, but they are generally considered to have little effect on clotting in vivo.
- Dextrans are considered more likely to cause clotting abnormalities than gelatins and associated allergic reactions have also been reported. Acute renal failure has also been reported with one type of dextrans solution (Dextran 40).
- High molecular weight HES solutions are most likely to cause multifactorial dose-dependent coagulopathy; at the time of writing tetrastarch is considered the safest HES solution in this respect. Allergic reactions occur very infrequently with HES solution use but they have been reported.

Indications

Short-term treatment for hypovolaemia:

Following attempts at fluid resuscitation using replacement crystalloids alone if the latter has proved ineffective. Some crystalloid therapy is usually continued in these cases and colloid therapy is typically discontinued first.

From the outset in animals in which there are specific indications: 'capillary leak syndrome'; hypoproteinaemia/hypoalbuminaemia.

More long-term use:

It is not common for patients to remain on long-term colloid therapy. However potential indications include:

- To minimise interstitial oedema in the presence of low plasma colloid osmotic pressure due to hypoproteinaemia; (in chronic hypoproteinaemia, the osmotic pressure of the interstitial compartment will also fall, increasing the likelihood of oedema).
- Systemic vasculitis or 'capillary-leak syndrome' (e.g. SIRS, sepsis)

A typical rate for on-going use is 1 ml/kg/h and it is generally recommended not to exceed 24 ml/kg/day.

Refractometer effects

Synthetic colloid administration will affect plasma total solids (TS) and urine specific gravity (USG) when measured using a refractometer:

The total solute concentration of most synthetic colloids is approximately 40 g/l so following administration, TS trends towards 40 irrespective of the animal's serum total protein concentration and refractometry is no longer a surrogate of plasma colloid osmotic pressure (COP). Refractometric TS may be lower than the true plasma total protein concentration in an animal with a plasma total protein concentration of more than 40 g/l.

USG increases dramatically following colloid administration and is no longer an indicator of renal concentrating ability.

Podcast on crystalloids and colloids for resuscitation

For a recent (January 2015) free podcast episode which discusses crystalloids and colloids in some depth click HERE. A transcript of the episode is also available on the website.

http://www.veteccsmalltalk.com/episode/9

The fluid plan

There is no set protocol for fluid therapy in any given situation and often the specific approach is determined both by the fluids and equipment available, and by the experience and preferences of the clinician involved.

A number of questions should be answered when determining the fluid plan:

Is fluid therapy indicated? If so, what is/are the indication(s)?
Which fluid(s) is/are appropriate?
How should the fluid therapy be administered?
How much should be given and for how long?
Are there specific considerations for the patient in question?

It is also very important that adequate monitoring is performed both to ensure that fluid administration is successful and safe, and to assess the patient's response.

The two most common indications for parenteral fluid therapy are:

1) **To correct perfusion deficits in hypovolaemia**: is the patient hypovolaemic, and if so, is this mild, moderate or severe?

2) **To replace fluid deficits in dehydration**: is the patient dehydrated and if so what is the estimated percentage dehydration?

Correction of electrolyte and acid-base abnormalities are other albeit less common indications for parenteral fluid therapy.

Hypovolaemia

Aim: restore the effective circulating intravascular volume and thereby restore adequate tissue perfusion.

Basic approach:

Think in terms of bolus administration and repeated reassessment of perfusion.

The peripheral intravenous route is typically used; the intraosseous route is an invaluable alternative in some cases (e.g. small patient size, severely collapsed vasculature).

- Use one or more of the shortest but largest bore catheters possible to minimise resistance to fluid flow

Intravenous fluid boluses are administered until end-points suggestive of acceptable systemic perfusion are achieved

- Boluses are given via infusion pump, free flow or under pressure (pressure bag or manual squeezing) as appropriate

Performed over a short period of time – usually a few minutes to an hour but sometimes longer

May involve the use of both isotonic crystalloids and synthetic colloids (plus blood products or hypertonic saline if available)

Replacement isotonic crystalloids are the first choice in the majority of cases
Overall approach tailored to the requirements of each individual patient

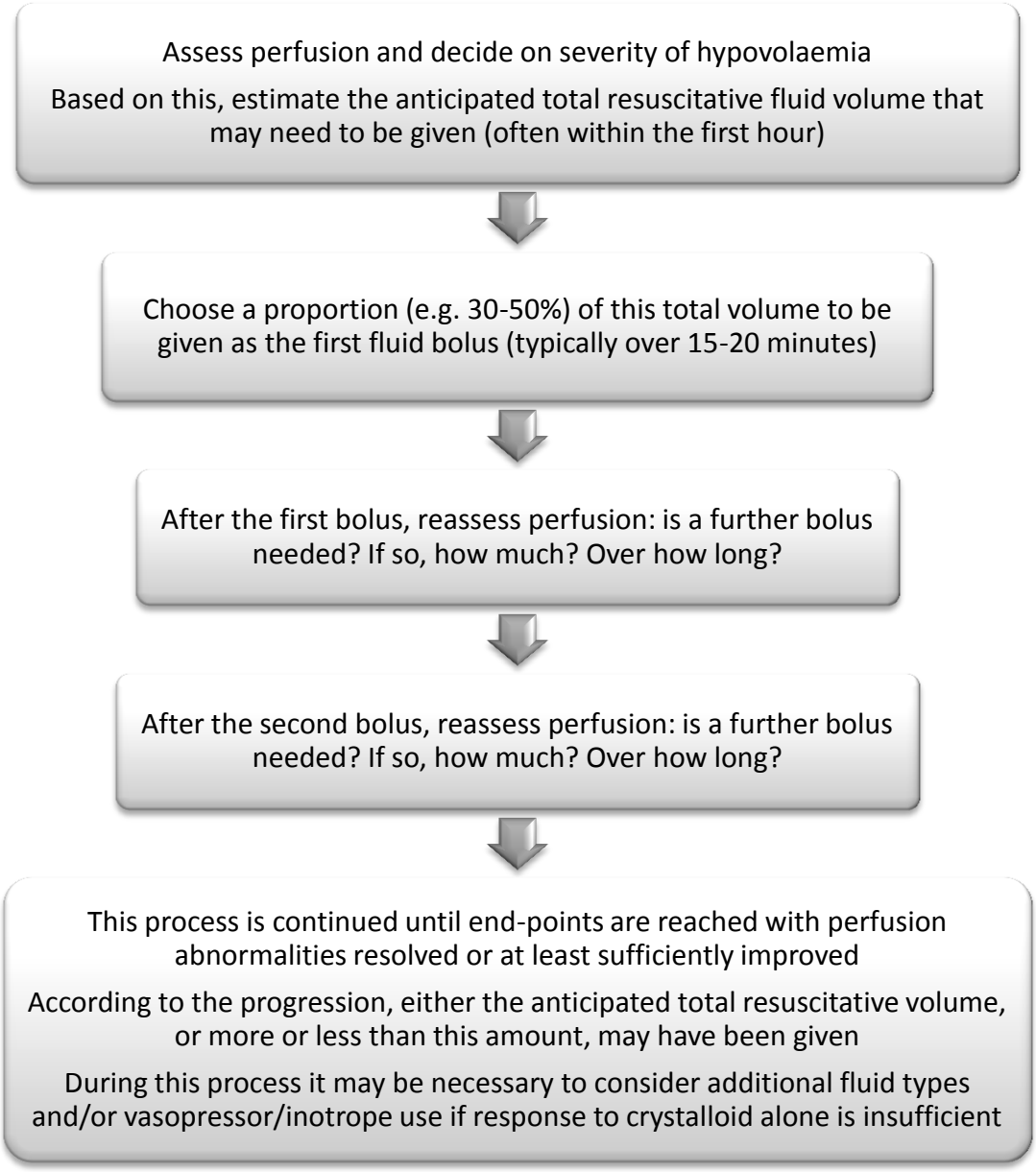
Dosing guidelines in hypovolaemia

Replacement isotonic crystalloids

	Size of first fluid bolus (ml/kg) (usually over 15-20 minutes)	Anticipated total resuscitative fluid volume (ml/kg) (Often within the first hour)		
Severity of hypovolaemia		Mild	Moderate	Severe
Dogs	**10-40**	**20-40**	**40-60**	**60-90**
Cats	**5-20**	**10-20**	**20-40**	**40-60**

Synthetic colloids

Dogs: 5-10 ml/kg boluses (traditionally up to a total of 20 ml/kg)
Cats: 2-5 ml/kg boluses (traditionally up to a total of 10 ml/kg)



If the patient's presenting history and subsequent assessment suggests concurrent dehydration, this must be taken into account with respect to on-going fluid therapy. Some clinicians subtract the volume of crystalloid administered during treatment of hypovolaemia from the calculated replacement deficit; others subject this to benign neglect on the basis that "the kidneys will work it all out in the end!".

Special considerations

The priority in treating hypovolaemic patients is to restore an effective circulating volume. Nevertheless there are some patient populations in which a less aggressive approach is warranted with smaller fluid boluses being used and/or fluid boluses being given over a longer period of time. Occasionally it is tolerated that a patient remains borderline hypovolaemic rather than risk fluid overload.

Scenarios warranting specific consideration include:

Recent or active haemorrhage
Lung pathology
Heart disease
Raised intracranial pressure
Chronic anaemia
Renal insufficiency

Recent or active haemorrhage

Much has been written about the 'best' approach to the resuscitation of haemorrhagic hypovolaemia. Most of this has been based on work done in human patients and in experimental animals. Essentially fluid therapy in haemorrhagic shock aims to:

- Restore intravascular volume
- Restore blood-oxygen carrying capacity
- Normalise coagulation status

Which fluid to use?

In terms of isotonic crystalloid versus synthetic colloid, there is no evidence-based consensus that one is 'better' than the other here and both have pros and cons. The majority of clinicians use a replacement isotonic crystalloid in the first instance and the potential for synthetic colloids to cause dose-dependent coagulopathy must not be overlooked in patients already bleeding.

Haemostatic resuscitation

As well as the potential for anaemia, bleeding patients have various reasons to be coagulopathic, both primarily, i.e. if a coagulopathy is the cause of bleeding in the first place and secondarily – for example due to inflammation from trauma; hypothermia ('lethal triad' of hypothermia, acidaemia and coagulopathy); clotting factor consumption; and dilutional coagulopathy from resuscitative fluid already administered. 'Haemostatic resuscitation' describes the aggressive early use of packed red blood cells and clotting products, a practice which is increasingly preferred in human patients as a way of restoring, or at least minimising impact on, oxygen-carrying capacity and coagulation status while improving intravascular volume. Crystalloids after all do not form blood clots or promote haemostasis; they may also contribute to trauma-induced coagulopathy by causing dilutional coagulopathy. They also do not provide any oxygen-carrying capacity. The same is true of synthetic colloids which in addition may also actually cause a dose-dependent coagulopathy by additional mechanisms. However lack of resources means that this approach is unlikely to be realistic in most veterinary environments in which avoiding both synthetic colloid use if possible and overzealous crystalloid administration may be sensible.

Hypotensive resuscitation

Haemorrhagic hypovolaemia is one example in which the concept of 'permissive hypotension' or 'hypotensive resuscitation' has been put forward as opposed to more standard 'normotensive resuscitation'. This involves titrating volume resuscitation to a sub-normal end-point that should nevertheless improve tissue oxygen delivery enough to maintain organ viability until such time as

bleeding can be controlled. So for example in patients in which systemic arterial blood pressure can be reliably monitored, one may usually aim to resuscitate to a mean arterial pressure of 80 mmHg (or a systolic blood pressure of 100 mmHg); in permissive hypotension the end-point might be MAP 65 mmHg (or systolic 80 mmHg).

By avoiding overzealous fluid resuscitation which targets normotension, the hope is to preserve the first and often best clot at any sites of bleeding. The need to control bleeding as soon as possible by either temporary (e.g. tourniquet, haemostatic agent) or permanent (i.e. surgical intervention) measures is important to stress although in some patients bleeding will be self-limiting. More aggressive fluid resuscitation is then used as required once haemorrhage is controlled.

In bleeding patients with head trauma, normotensive resuscitation would seem most rational to ensure adequate cerebral perfusion pressure and thereby try to minimise secondary brain injury; the importance of CPP in brain injury has a strong evidence base at least in human patients if not yet in clinical dogs and cats. This may also be true for spinal cord perfusion pressure in spinal cord injury but more evidence is needed.

Note that permissive hypotension is usually only considered in patients with on-going haemorrhage in which it is planned to intervene to control the bleeding and this technique is used to maintain organ viability in the meantime. This is a patient population that is encountered much less frequently in veterinary medicine than in human medicine so care is needed not to over-apply this resuscitative technique the evidence base for which is still scarce in humans, even more so in dogs and cats.

Lung pathology

The lungs have extensive capacity to cope with fluid but pathological lungs may be more prone to oedema than healthy lungs. This scenario is encountered most commonly in the form of pulmonary contusions following thoracic trauma. Animals suffering from severe trauma (thoracic or non-thoracic) or from other causes of shock may also develop acute lung injury (ALI) or acute respiratory distress syndrome (ARDS); this is especially true for cats.

In hypovolaemic animals with lung pathology that do not respond adequately to conservative crystalloid boluses, a synthetic colloid may prove effective. However in some types of lung pathology, the pulmonary vasculature can become leakier to colloid molecules despite their large size. Once the colloid molecules move into the pulmonary interstitium they may worsen pulmonary oedema and may persist there for some time. Nevertheless it is not possible to predict in advance whether this will occur and it is therefore recommended to assess the patient's response to a colloid bolus and discontinue this therapy if respiratory status worsens as a result.

Heart disease

Patients with heart disease requiring fluid therapy need to be treated extremely carefully. Administration of fluids will increase the circulating volume and the diseased heart may not be able to cope with the added load resulting in congestive heart failure. Hypovolaemia must still be treated but more conservatively than in an animal without heart disease, and fluid therapy should be discontinued as soon as possible.

The majority of dogs with clinically significant heart disease will have a murmur on auscultation. However failure to identify a murmur (or gallop sound) does not rule out clinically significant heart disease.

Thoracic radiography and especially echocardiography may help guide therapy by providing further information with respect to left atrial enlargement and therefore the likely ability of the patient to cope with fluid therapy.

Once hypovolaemia is corrected, fluid therapy is generally discontinued as soon as possible in animals with heart disease. In patients that require rehydration and maintenance fluid therapy, strategies such as using a low rate (0.5-1 mL/kg/h) infusion of 0.45% (half strength) saline or subcutaneous fluid administration should be considered. These patients should be monitored very closely for signs of fluid overload.

Raised intracranial pressure

Causes of intracranial hypertension include:

- Head trauma
- Intracranial masses
- Severe seizures

Overzealous intravenous fluid therapy can lead to cerebral oedema and thereby exacerbate existing raised intracranial pressure. However the priority in protecting the brain from further secondary injury is to ensure that cerebral perfusion is adequate. Cerebral perfusion is highly dependent on systemic blood pressure so the approach here is to rapidly correct hypovolaemia but then discontinue aggressive fluid therapy as soon as possible. This is most often a concern in patients with both hypovolaemia and head trauma; hypertonic saline can prove very useful in such patients.

Chronic anaemia

Depending on the severity, animals with chronic anaemia may already be in a state of volume overload and are therefore at greater risk from aggressive fluid therapy. In addition fluids will cause haemodilution; although the same number of red blood cells is still circulating in the body, a lower PCV is likely.

Renal insufficiency

Fluid therapy is an extremely important consideration in patients with renal insufficiency. This is especially the case in animals with acute renal failure that frequently have either oliguria (reduced urine production) or polyuria (excess urine production). Patients with oliguric renal failure are vulnerable to fluid overload (as well as hyperkalaemia) while those with polyuria are susceptible to dehydration and hypokalaemia.

Monitoring of ‘ins and outs’ is very important in these cases, and intravenous fluid administration allows regular adjustment of ‘ins’ in response to ‘outs’. Animals with chronic renal insufficiency may be

anaemic and in some cases this can be moderate-to-severe; these patients may therefore be in a state of volume overload. Although this is unlikely to be a significant consideration when subcutaneous or low rates of intravenous fluid therapy are administered, it may be of importance during aggressive volume resuscitation.

Podcast answering some questions about fluid therapy

For a free podcast episode (January 2015) answering some questions about fluid therapy in patients with pulmonary contusions, with heart murmurs and exposed to renal toxins see HERE.

http://www.veteccsmalltalk.com/episode/7

Dehydration

Aim: to replace deficits from all fluid compartments that are affected; this is mainly the interstitial and intracellular compartments in dehydration.

Basic approach:

- Corrected over a longer period of time than hypovolaemia – typically 12-48 hours depending on the severity and rate of onset
- Replacement isotonic crystalloids used alone

Rehydration is usually performed via the **intravenous** route. In some cases, **subcutaneous** fluid therapy may be a reasonable option.

Fluid requirement = Replacement volume + Maintenance requirement + On-going losses
over chosen period of time

The initial fluid plan calculated for a dehydrated patient is an approximation and both the rate and the type of fluid used need to be reassessed. A range of different factors are taken into account that includes:

- Changes in physical examination parameters and especially in other measures of hydration – PCV/TS, body weight, urea/creatinine
- Whether the animal is eating/drinking (if allowed)
- A subjective assessment of the degree of on-going losses

Due attention must also be paid to the provision of supplementary potassium in particular in appropriate cases.

Replacement volume

Replacement volume (fluid deficit, mL) = % dehydration x body weight (kg) x 10
Percentage dehydration estimated on the basis of physical examination.

Maintenance requirement

Maintenance fluid requirements are related to metabolic rate which is a function of body surface area and varies with species and breed, and especially with age and size.

Formulae are available for calculating maintenance fluid requirements in dogs and cats. Depending on which formula is used, different figures may be obtained. Probably the most common recommendations are as follows:

- In animals weighing between 2-50 kg, use ([BW (Kg) x 30] + 70) mL/day
- In animals weighing < 2 Kg or > 50 Kg, use [$BW^{0.75}$ (Kg) x 70] mL/day

However, the fact that there are various different formulae perhaps illustrates that there is no definite consensus on which is the 'most correct'. An empirical approach with regular reassessment of the patient is therefore reasonable and practical.

Guidelines for maintenance requirements:

- Fully grown dogs: 1.5 mL/kg/h (larger dogs) up to 4 mL/kg/h (very small/toy breed dogs)
- Fully grown cats: 2-3 mL/kg/h
- Paediatric patients: 4-8 mL/kg/h; smaller and/or younger towards the upper end, larger and/or older towards the lower end.

Maintenance requirements for overweight animals should be calculated using a reduced body weight.

On-going losses

These are on-going losses such as vomitus and diarrhoea that occur over and above normal losses accounted for in maintenance requirements. It is practically very difficult, and often inherently inaccurate, to try and quantify these objectively and therefore one solution is to estimate the contribution from these additional on-going losses in terms of multiples of the patient's maintenance requirements. For example:

- A patient with no additional on-going fluid losses has no additional contribution to the initial fluid plan
- A patient with occasional vomiting daily may have half a maintenance requirement added to the initial fluid plan
- A patient with multiple episodes of vomiting daily may have an extra maintenance requirement added to the initial fluid plan
- A patient with multiple episodes of vomiting and profuse diarrhoea daily may have two extra maintenance requirements added to the initial fluid plan

These are very much guidelines only and on-going losses are re-estimated on a daily basis. Although this approach is somewhat subjective, as long as on-going losses and hydration parameters are reassessed daily and fluid rates are adjusted accordingly, this approach is both valid and clinically practical.

Example calculations

Example 1

A 3.5 kg adult female neutered domestic short-hair cat presents with a 2-day history of anorexia and lethargy of unknown cause. She is assessed as being 8% dehydrated, rehydration is to be performed over 24 hours, and there are no extra on-going losses evident initially.

Replacement volume (fluid deficit, ml) = % dehydration x body weight (kg) x 10
= 8% x 3.5 kg x 10
= 280 ml

Maintenance fluid rate = 2 ml/kg/h
Maintenance requirement over 24 hours = 2 ml x 3.5 kg x 24 h = 168 ml
No additional on-going losses beyond those accounted for in maintenance requirement.

Fluid requirement = Replacement volume + Maintenance requirement + On-going losses over chosen period of time

Fluid requirement = 280 ml + 168 ml + 0 ml = 448 ml over 24 hours
= approx 18.7 ml/h
= 5.3 ml/kg/h

Example 2

A 20.0 kg adult male neutered crossbreed dog presents with a 2-day history of anorexia, lethargy, multiple episodes of vomiting and passing watery bloody diarrhoea. He is assessed as being 10% dehydrated, rehydration is to be performed over 12 hours, and significant additional on-going losses are anticipated.

Replacement volume (fluid deficit, ml) = % dehydration x body weight (kg) x 10
= 10% x 20.0 kg x 10
= 2000 ml

Maintenance fluid rate = 2 ml/kg/h
Maintenance requirement over 12 hours = 2 ml x 20.0 kg x 12 h = 480 ml

Two extra maintenance requirements are added to account for the anticipated on-going losses.
On-going losses = 2 x 480 mL = 960 ml

Fluid requirement = Replacement volume + Maintenance requirement + On-going losses over chosen period of time

Fluid requirement = 2000 ml + 480 ml + 960 ml = 3440 ml over 12 hours
= approx 286.7 ml/h
= 14.3 ml/kg/h

Subcutaneous fluid therapy

Only isotonic crystalloid solutions should be used and the total volume is typically divided between several sites.
Depending on the species in question, a dose of 10-20 mL/kg is usually used and this route of administration is therefore most suitable for smaller dogs and cats and for exotics.

Examples in which this route may be appropriate:

- Mild dehydration
- Owners unable (or unwilling) to pay for intravenous fluid therapy
- Owners reluctant to leave their pets at the clinic
- Intermittent use to provide fluid support in chronic illnesses such as chronic renal failure.

The sole use of subcutaneous fluid therapy is inappropriate in patients with hypovolaemia as absorption is too slow due to poor peripheral perfusion.

Complications of skin sloughing, infection and pain are all potentially associated with repeated use of this route of fluid therapy. The fluid should be warmed to body temperature as cold fluids will cause pain and vasoconstriction of the skin vessels slowing down the rate of absorption.

Another route of administering fluid replacement that has had some consideration in human medicine and for which there is some anecdotal experience in veterinary patients is the rectal route (proctolysis).

Monitoring

Given the risk of volume overload with indiscriminate fluid administration, it is important to monitor animals receiving fluid therapy. The type and intensity of monitoring should be decided based on how susceptible each individual patient is thought to be to fluid overload.
It is increasingly being realised that more is not always better when it comes to fluid therapy, especially in certain populations where keeping the patient on the 'dry' side may be less harmful than excessive fluid administration. The relative pros and cons of keeping patients 'wetter' or 'drier' according to their disease states remains to be clarified in humans and even more so in dogs and cats.

There are two aspects to monitoring fluid therapy. The first is to monitor that the abnormalities for which the fluid is being administered are improving, i.e. **perfusion or hydration deficits are resolving**; rehydration is usually monitored using both clinical pathology parameters and body weight.

The second aspect is to monitor for **volume overload**, i.e. excessive fluid administration beyond that which the patient can excrete. Regular physical examination is the predominant method of monitoring for volume overload.

- Respiratory rate, effort and lung auscultation to detect pulmonary oedema
- Evidence of peripheral tissue oedema (e.g. chemosis, facial oedema, distal limb oedema)
- Serous nasal discharge

Urine output has a role in the monitoring of fluid therapy, with objective quantification indicated in specific patient populations.

Volume overload is treated by discontinuing or at least reducing the rate of fluid therapy and administering diuretic therapy if sufficiently concerned.

Central venous pressure

Central venous pressure (CVP) measurement requires an in-dwelling central venous catheter and is greatly facilitated by having a transducer and multi-parameter monitor; however it can be achieved using an improvised manometer. The pressure within the right atrium is measured and this is used as a proxy of the pressure in the central venous system from which is inferred the patient's intravascular volume status – it is essential to realise that CVP is a pressure not a volume and so for example a normovolaemic patient with cardiac dysfunction and low cardiac output (e.g. as may occur in some septic patients) can have a high CVP despite being volume deplete.

There is much debate about the usefulness of CVP and whether it is more helpful as a proxy of volume status or of volume responsiveness. The consensus in human medicine at this time appears to be that while there is some contested evidence that CVP is useful as a marker of fluid tolerance/safety (i.e. how likely you are to overdo it/overload the patient resulting in especially pulmonary oedema) its value is even more limited as a marker for fluid responsiveness (i.e. if and how well the patient may respond positively to a fluid challenge).

Central venous pressure monitoring is most robust using trends rather than single values, and may be especially helpful in cardiac patients. There are significant practical issues with central venous pressure monitoring and it not performed routinely outside of referral centres.

- Measurements from 0-5 cm H_20 are considered normal though it is the trend that is most important
- A rapid increase of 3-5 cm H_20 during fluid therapy suggests possible fluid overload and decreased fluid administration is indicated

Placement of a jugular catheter is not considered essential in the first phase of fluid resuscitation. Central venous catheter placement requires time and experience and fluid resuscitation should not be delayed in order to achieve this access.

ANALGESIA FOR THE EMERGENCY PATIENT

General Discussion

"The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment" (International Association for the Study of Pain 1994).

The American Veterinary Medical Association in 2001 stated "The AVMA believes that animal pain and suffering are clinically important conditions that adversely affect an animal's quality of life. Drugs, techniques, or husbandry methods used to prevent and control pain must be tailored to individual animals and should be based, in part, on the species, breed, age, procedure performed, degree of tissue trauma, individual behavioural characteristics, degree of pain and health status ."

Adverse Consequences of Pain

Pain is associated with a number of **adverse physiological and psychological responses** including:

- Unnecessary suffering
- Altered mentation: anxiety, agitation; dullness, depression
- Reduced food intake – may slow recovery
- Prolonged recumbency
- Self-mutilation
- Impaired respiration
- Sensitisation to noxious stimuli
- Excessive sympathetic stimulation, enhanced catabolism, delayed wound healing, immune suppression
- Inability to monitor patients effectively due to pain-induced physiological changes
- Untreated acute severe post-operative pain increases the chances of developing chronic pain

Adequate pain management is therefore both about improving both patient welfare and physical health.

Pain Assessment

In 2011 it was the Global Year Against Acute Pain in human medicine which had the motto: “Anticipate, Assess, Alleviate”. In veterinary medicine we should amend this to “Anticipate, Assess/Assume, Alleviate”.

Pain assessment in animals involves a combination of sign recognition, patient interaction, clinical experience, and anthropomorphism*.

(* = attributing human characteristics to animals)

Signs of Pain

The signs that an animal in pain may exhibit depend on various factors including:

- The source, severity and duration (acute, chronic) of pain
- Individual patient variability – age, species, breed, tolerance, temperament

Potential signs of pain include:

- Consistent response on palpation of painful area
- Poor appetite
- Restlessness (especially dogs); dullness, depression and lack of activity (especially cats)
- Looking, licking, biting or scratching at painful area; self-mutilation
- Salivating
- Vocalisation: dogs – growling, whining, groaning; cats – purring, growling, hissing
- Reduced grooming behaviour
- Altered gait and reluctance to walk
- Abnormal posture (especially cats who often sit with a hunched sternal posture rather than lying curled in lateral recumbency)
- Reluctance to sleep
- Uncharacteristic behaviour (aggression or affection) towards humans
- Inappropriate urination and/or defaecation
- (Unexplained tachycardia, tachypnoea/panting, hypertension, or pupillary dilation)

Cats are often much less demonstrative than painful dogs and sick animals in general may be unable to show expected behavioural signs of pain. In addition, physiological parameters such as heart rate and respiratory rate are not consistently reliable as indicators of pain.

Differentiating pain from other stress (e.g. fear, anxiety, claustrophobia) as well as from dysphoria/narcotisation can be challenging. Differentiating pain from anaesthesia-related behaviours ("emergence delirium") is usually less challenging.

If it is not clear whether an animal is in pain, the patient should always be given the benefit of the doubt, and analgesic drugs carry minimal risk as long as they are used judiciously. A low testing dose can be given and the patient monitored for a favourable response.

Pain Scales

Pain scales can be used as a means of trying to improve objectivity by quantifying pain for example to:

- Potentially improve reliability of (re)assessment
- Allow analgesic efficacy to be assessed and drug doses titrated
- Provide better consistency for hospitalised patients; facilitate more long-term pain management of hospitalised patients by trying to provide some consistency and hand-over between different staff members working on consecutive shifts.
- Facilitate statistical analysis and clinical research

Pain assessment is always going to be subjective in the non-communicating patients that veterinary staff deal with but multidimensional composite pain scoring systems try to reduce the degree of subjectivity and therefore improve consistency, reliability and hopefully patient welfare.

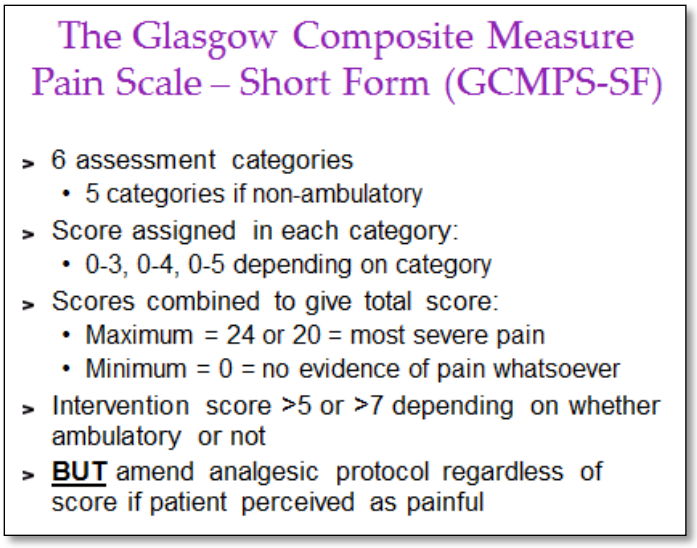
The Glasgow Composite Measure Pain Scale (GCMPS) (Holton et al, 2001) is the only pain scale validated for assessment of acute pain in dogs thus far. It is a behaviour-based system based on a structured questionnaire that includes clinical observation, assessment of spontaneous and evoked behaviour and animal-observer interaction. The questionnaire is structured around seven categories: posture, activity, vocalisation, attention to wound/painful area, demeanour, mobility and response to touch. Based on the score obtained at the end, it is possible to quantify the degree of pain the animal is experiencing.

Other composite pain scoring systems exist but GCMPS is considered most scientifically derived, validated and reliable. It was derived using psychometric principles and statistical methodologies following approach taken by Melzack (1975); this 1975 paper has been modified/revised but has stood the test of time. The original GCMPS was developed into an interval level scale (Morton et al, 2005) and then a Short Form and intervention score developed for greater clinical usability (Reid et al, 2007). It is noteworthy that while the GCMPS is the most widely used and reported system and has been applied to pain from any cause, much of what has been reported relates to acute post-operative pain and also chronic osteoarthritic pain.

- Morton et al, 2005:
    - Developed then validated scaling model
    - Validation groups (4 x 20 dogs) included medical group but no further details regarding their medical conditions
- Reid et al, 2007:
    - Developed Short Form (GCMPS-SF) and intervention score
    - 122 surgical dogs

[Papers:

Holton L, Reid J, Scott EM, et al. Development of a behaviour-based scale to measure acute pain in dogs. *Vet Rec* 2001. 148:525-531.
Melzack R. The McGill pain questionnaire: major properties and scoring methods. *Pain* 1975. 1:277-299.
Morton CM, Reid J, Scott ME, et al. Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. *Am J Vet Res* 2005. 66:2154–2166.
Reid J, Nolan AM, Hughes JML, et al. Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. *Animal Welfare* 2007. 16(S):97-104.]



Other examples include Colorado State University Canine and Feline Pain Scales. The Colorado Feline Pain Scale is probably the feline pain scoring system with which there is the greatest clinical experience. In December 2014 the Glasgow Composite Measure Pain Scale for Acute Pain in Cats: CMPS – Feline was published which is a revised version of an earlier version from 2010. More clinical experience clearly needs to be obtained with this new system and the authors themselves are intending to further develop the scale by incorporating a facial expression component* with the intention of improving its sensitivity.

[* Pilot study: Holden E, Calvo G, Collins M, et al. Evaluation of facial expression in acute pain in cats. J Sm Anim Pract 2014. 55(12):615-621.]

Please see Appendix 1 for examples of pain scales.

Pain Pathways

A basic knowledge of the pain pathways is essential to understand the modes of action of available analgesics and the rationale behind multimodal therapy. The pain pathway essentially consists of **peripheral** and **central** components. Peripheral tissue receptors (nociceptors) detect the painful stimulus and the subsequent signal is then conducted via primary afferent nerve fibres to the dorsal horn of the spinal cord or to the cranial nerve nuclei. Nociceptive signals are processed (modulated) first in the spinal cord and subsequently in higher centres resulting in conscious pain perception.

- **Transduction** is the translation of physical energy (noxious stimuli) into electrical activity at the peripheral nociceptor.
- **Transmission** is the propagation of nerve impulses through the nervous system. Afferent sensory fibers consist of myelinated A-delta fibers which conduct fast pain, and non-myelinated C fibers which conduct slower dull pain.
- **Modulation**: processing (amplification or inhibition) of stimuli within spinal cord dorsal horn cells.

- **Perception**, not considered a part of the nociceptive process, results from integration of the noxious stimuli in the thalamocortical, reticular, and limbic regions of the brain to produce the final conscious subjective and emotional experience of pain.

Injury to peripheral tissues is often associated with inflammatory pain and injury to the central nervous system associated with neuropathic pain.

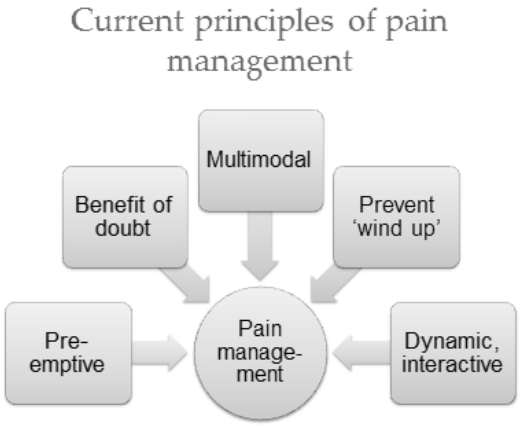
Sensitisation

Following injury there is increased sensitivity to further noxious stimulation due to changes in nervous system processing; this is referred to as sensitisation or 'wind up'. Sensitisation may occur in either or both of the peripheral and central components of the pain pathway and may result in:

- **Continued pain**
- **Hyperalgesia**: an exaggerated responsiveness to a given noxious stimulus; and
- **Allodynia**: stimuli that are normally innocuous become painful

Inflammatory mediators are involved in central and especially peripheral sensitisation; the glutamate-activated N-methyl-D-aspartate (NMDA) receptor is very important in central sensitisation.

In practical terms, once sensitisation is under way conscious perception of pain is greater, it is more difficult to control and higher drug doses are required. It is therefore *preferable to try and prevent pain rather than to merely treat it once it is established.* A significant proportion of emergency patients are already in pain at initial presentation. In order to minimise sensitisation, pain management should be instituted as soon as possible and, once the pain is under control, the patient kept on a level pain-free plateau. All animals going on to have operative procedures performed will benefit from adequate preoperative analgesia, i.e. in advance of the significant noxious stimulation resulting from surgical intervention. And it is clearly important to bear in mind the onset of action the agent you are using has to prevent noxious stimulation before analgesic efficacy has been achieved (e.g. following subcutaneous administration NSAIDs take 0.5-2.5 hours to reach maximum plasma concentration depending on the specific agent being used).



Analgesic Agents

Balanced analgesia involves the use of one or more appropriate analgesics (*multimodal therapy*) in an effective dosing regimen given by the appropriate route(s). **By combining multiple analgesic drug classes or techniques to target different points along the pain pathway** multimodal therapy should offer:

- Additive analgesic effects
- A reduction in the doses of individual drugs
- Reduced frequency and severity of adverse side-effects

Analgesic agents that are commonly available in emergency clinics in countries in which veterinary medicine is more developed include:

- Opioids
    - Tramadol
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Local analgesic/anaesthetic agents
- Ketamine
- Medetomidine

An intuitive approach to pain management is based on thorough initial evaluation followed by regular reassessment of the patient and adjustment of the treatment protocol as indicated. This is especially relevant to the use of full agonist opioids which may be used at highly variable dose rates and dosing frequencies. As described later, non-pharmacological measures are also very important in pain management.

["Pain ladder", or analgesic ladder, is a concept originated by the World Health Organization (WHO) to describe its guideline for the use of drugs in the management of pain. It was originally applied to the management of cancer pain, but is now widely used by medical professionals for the management of all types of pain.

The general principle is to start with first step drugs, and then to climb the ladder if pain is still present. The medications range from household, over-the-counter drugs with minimal side-effects at the lowest rung, to powerful opioids.

Although this is a human medicine concept the principles can be extrapolated to veterinary patients.]

Opioids

In the author's opinion, all veterinary practices that may see animals in moderate to severe pain should have a full (pure) opioid agonist available, ideally morphine or methadone. These agents are extremely affordable, highly effective, and allow dose titration to effect. Although they need to be stored and administered in accordance with regulations for controlled drugs, this should not be considered an impediment to their use.

It is a **misconception that all opioids cause excitement or so-called 'morphine mania'** in cats; unfortunately this fear of excitement has been one of the reasons why practitioners have historically been hesitant to use opioids in cats. Such reports were based on early literature when excessive doses, far in excess of those required to provide analgesia, were administered to typically healthy patients.

Opioids (predominantly) act in the **central** component of the pain pathway. Most opioids used clinically are selective for the μ-receptor and are full (pure) agonists, partial agonists, or agonists-antagonists. They are the mainstay of pain management in the emergency patient and block central sensitisation. Opioids are also used in low doses for sedation or anxiolysis.

High doses of pure opioids in particular may result in dysphoria (vocalisation, anxiety, restlessness) that can be difficult to differentiate from on-going pain. Naloxone (or butorphanol) can be used to reverse the effects of full opioid agonists. Both respiratory depression and bradycardia are rarely seen as side effects of concern during opioid administration in clinical veterinary patients that are not under anaesthesia. Furthermore, pain itself can cause respiratory compromise and appropriate opioid administration can normalise respiratory status in such cases. Until adequately treated, pain can also confuse assessment of other parameters such as heart rate and blood pressure.

Dose rates, routes of administration and dosing frequencies of opioids in current use in emergency clinics are summarised in the table below.

Drug	Dogs	
	Dose / routes of administration	Dosing frequency
Morphine	0.1-1.0 mg/kg slow i.v., i.m. or s.c. 0.1-0.5 mg/kg/h CRI	prn, q 4 h
Methadone	0.1-1.0 mg/kg slow i.v., i.m. or s.c.	prn, q 4 h
Fentanyl	2.0-10.0 µg/kg slow i.v. 2.0-10.0 µg/kg/h CRI (after initial loading dose 2.0-10.0 µg/kg)	prn, q 20 min
Buprenorphine	0.01-0.02 mg/kg i.v., i.m. or s.c.	q 6-8 h
Butorphanol	0.1-0.6 mg/kg i.v., i.m. or s.c. 0.05-0.2 mg/kg/h CRI	prn, q 1-4 h
Naloxone (antagonist)	0.01-0.1 mg/kg slow i.v. to effect	prn

Drug	Cats	
	Dose / routes of administration	Dosing frequency
Morphine	0.1-0.5 mg/kg slow i.v., i.m. or s.c. 0.05-0.2 mg/kg/h CRI	prn, q 6 h
Methadone	0.1-0.5 mg/kg slow i.v., i.m. or s.c.	prn, q 6 h
Fentanyl	1.0-5.0 µg/kg slow i.v. 1.0-5.0 µg/kg/h CRI (after initial loading dose 1.0-5.0 µg/kg)	prn, q 20 min
Buprenorphine	0.01-0.02 mg/kg i.v., i.m., s.c. or o.t.m.	q 6-8 h
Butorphanol	0.1-0.6 mg/kg i.v., i.m. or s.c. 0.05-0.2 mg/kg/h CRI	prn, q 1-4 h
Naloxone (antagonist)	0.01-0.1 mg/kg slow i.v. to effect	prn

CRI – constant rate infusion; i.m. – intramuscular; i.v. – intravenous; prn – pro re nata (as needed); s.c. – subcutaneous

Morphine

- Gold standard analgesic for moderate-severe pain
- Full µ-agonist
- Onset of action is usually 10-15 min (or less) following intravenous or intramuscular administration
- Also extremely useful as an anxiolytic in respiratory distress
- Vomiting (both dogs and cats) is more likely than with other opioids and will further exacerbate raised intracranial or intraocular pressure – avoid in patients where this is of concern
- Rapid intravenous administration may cause signs associated with histamine release (transient vasodilation and hypotension) – slow intravenous boluses or a constant rate infusion recommended
- (Preservative-free morphine has been the traditional pure opioid used for epidural analgesia.)

Methadone

- Full μ-agonist (may also have an effect as a non-competitive NMDA receptor antagonist)
- Same or greater potency as morphine
- Sedative and dysphoric effects are reportedly less marked than with morphine and it does not typically induce emesis
- Does not cause histamine release following intravenous administration
- Not usually recommended to be used as a constant rate infusion due to variable half-life and potential to accumulate – but there is clinical experience with this route
- Panting (due to effects on the thermoregulatory centre) occurs much more commonly in dogs than it does with morphine and this may complicate clinical assessment; the author has not noticed tachypnoea or open-mouth breathing in cats following methadone administration.
- There is now a methadone preparation licensed in Europe for use in dogs for analgesia and premedication (Comfortan® 10 mg/ml, Eurovet Animal Health Ltd)

Fentanyl

- Full (pure) μ-agonist
- Very potent (50 times more potent than morphine)
- Rapid onset (seconds-minutes) and short duration (10-20 minutes depending on dose) of action therefore very amenable to titration
    - After prolonged administration or high doses, duration of action is significantly prolonged at the tissues become saturated
- Can be used as one-off bolus (for example at induction or to facilitate procedures), intermittent boluses or as a constant rate infusion
- Give slowly intravenously (rapid administration can cause severe bradycardia); severe bradycardia will likely respond to atropine
- Patients on fentanyl infusions must be monitored closely for bradycardia or respiratory depression

[Transdermal fentanyl patches are available but will not be discussed here. Very recently a transdermal fentanyl solution has been licensed in Europe for use in dogs following major orthopaedic or soft tissue surgery. It may provide up to 4 days analgesia after a single topical application.]

Buprenorphine

- Partial μ-agonist and a κ-antagonist
- Slow onset of action (slow to associate with its receptor) that may be up to 45 min – therefore not useful for rapid management of pain; full opioids preferred in such cases
- Indicated for mild to moderate pain
- Appears to be especially effective as an analgesic in cats – *but please note comment above regarding delay in onset of action!*
- Licensed for use in dogs and cats

The mixed agonist-antagonist actions of buprenorphine mean that doses above a certain level may be progressively less effective (i.e. buprenorphine has a bell-shaped dose/response curve with a ceiling effect). This means that in theory there is limited capacity to increase the administered dose of buprenorphine in an animal that remains painful. However, the ceiling *may* be higher than the typical clinical dose range used and this may therefore be more of a theoretical than a real concern. Increasing doses reportedly increase the duration of effect but do not increase the analgesia achieved.

Buprenorphine is a competitive μ-agonist that is reported to have strong receptor affinity and in theory clinical doses of alternative opioids are therefore unlikely to be effective for a variable but lengthy period of time, i.e. until the buprenorphine has detached from the receptors. However, some 'experts' question whether this is relevant at clinical doses and the author's clinical experience suggests that full agonists can be used effectively much sooner than traditionally thought possible; this may be due to surplus receptors that are free to bind to the full agonist or potentially because the full agonist displaces some of the buprenorphine from receptors.

[A small number of reports at the time of writing suggest that even allowing for the delay in absorption following subcutaneous administration, the use of this route may be less efficacious in cats that intravenous or intramuscular use of buprenorphine.]

A subcutaneous preparation of buprenorphine that reportedly has a 24-hour duration of action and only requires once daily dosing has very recently been licensed in the USA.
A sustained-release formulation of buprenorphine designed to give 72 hours analgesia after subcutaneous administration has been tested in cats having ovariohysterectomy and there is some clinical experience with it in the United States with both cats and dogs (Buprenorphine-SR available from ZooPharm®).

Oral transmucosal buprenorphine:

Orogastric buprenorphine preparations are available for people but have not been widely used in veterinary medicine. However, 1-2 experimental reports in a small number of healthy cats report that *oral transmucosal* administration of injectable buprenorphine results in both very high bioavailability and very similar pharmacokinetics to the intravenous route. The solution is tasteless and does not typically cause salivation or nausea. Administration of buprenorphine under the tongue or into the side of the mouth may therefore a useful option in cats requiring continued short-term analgesia at home, either in addition to a non-steroidal anti-inflammatory agent or where the use of a non-steroidal anti-inflammatory agent is inappropriate. However it is worth noting that one study for example in 100 female cats undergoing ovariohysterectomy concluded that "IV and IM administration of buprenorphine provided better postoperative analgesia than SC or OTM administration of the drug and these routes of administration should be preferred when buprenorphine is administered to cats." (Giordano T, Steagall PV, Ferreira TH, et al. Postoperative analgesic effects of intravenous, intramuscular, subcutaneous or oral transmucosal buprenorphine administered to cats undergoing ovariohysterectomy. Vet Anaesth Analg 2010. 37(4):357-366.)

Bioavailability of o.t.m. buprenorphine is likely to be lower in dogs (due to more alkaline oral pH) necessitating the use of considerably higher doses than those used for intravenous, intramuscular or subcutaneous administration. The use of buprenorphine by this route using standard injectable formulations is therefore likely to be impractical in dogs.

Butorphanol

- μ-antagonist and a κ-agonist
- Onset of action of 15 to 20 minutes
- Probable ceiling effect
- **Clinically more useful for its sedative and antitussive effects than as a potent analgesic**
- Because it is a κ-agonist, it may be more effective for mild-moderate visceral pain than some other opioids (i.e. as there may be more κ receptors in the viscera than elsewhere); this may especially be the case for gastrointestinal pain. However it is unclear if visceral analgesia is achieved at typical clinical doses (e.g. 0.2-0.3 mg/kg) or requires higher doses (e.g. 0.8 mg/kg)
- May also be used to reverse sedation and respiratory depression associated with full opioid use (due to μ-antagonist activity)
- Licensed for use in dogs and cats

Tramadol

- Synthetic centrally-acting analgesic
- Complex interactions between opiate (primarily μ), serotonin and adrenergic receptor systems; (also has an effect as an NMDA receptor antagonist)
- At least one metabolite (*O*-desmethyltramadol; M1) is significantly active and may be essential in tramadol's opioid effect
- May be indicated for long-term home use in cases in which NSAIDs are contraindicated or insufficient alone. May also be the safest current choice in nursing dams post-caesarean section.
- Also reported to have antitussive activity
- Main clinically relevant side-effects are lethargy, sedation and nausea
- Potential for cardiovascular and respiratory depression may be greater following parenteral (intravenous) administration but is unlikely to be clinically relevant when used judiciously
- Naloxone will partially antagonise the effects of tramadol

The currently recommended dose range for dogs is 1-5 mg/kg q 6 -12 hours. A similar range is likely to be appropriate for cats but they should be started on the lower end of the dose range and/or upper end of the dosing interval, and then titrated upwards as necessary. However it is important to realise that there is still some uncertainty about the optimal dosing regime in veterinary patients. Experimental studies in healthy animals show that the pharmacokinetics of tramadol in veterinary patients is different to that in humans. In humans dosing is usually done every 4-6 hours and it may be that this frequency is appropriate in dogs and cats (i.e. more frequently than is typically currently used); moreover what doses are likely to prove effective at different intervals still remains to be clarified. Depending on geography, tramadol is reportedly available as various tablet strengths as well as other oral formulation types, an extended-release formulation, a combination preparation with paracetamol (acetaminophen)*, and an injectable preparation.

(* The oral preparation containing paracetamol should never be used in cats.)
(In people, seizures have been reported at therapeutic doses as a side-effect. The risk may be greater at higher doses or with concurrent administration of other drugs that may lower the seizure threshold.)

Titration

Full opioids – morphine, methadone, fentanyl – are typically the most appropriate analgesic agents for use in moderate to severe pain. Their efficacy, rapid onset of action, linear dose/response curve, and high index of safety make them highly suitable for titration in severe pain management.

The initial dose chosen should be guided by the severity of pain identified or suspected; intuitively, the same dose of the same drug cannot be appropriate in all situations. The patient should then be reassessed once the drug has had enough time to take effect and additional analgesia administered if indicated. Mydriasis is usually a sign of adequate opioid administration in a cat.

Clinically significant side effects of full opioids are rare in companion animals that are not under general anaesthesia and these concerns should not prevent administration of adequate analgesia.

Constant rate infusions

Constant rate infusions (CRI) of opioids (morphine in particular), as well as ketamine and lidocaine, are in widespread use as they offer clear advantages for pain management and most of the cases in question will have intravenous access available. Constant rate infusions avoid the peaks and troughs in plasma drug concentrations associated with intermittent boluses. They also provide more sensitive control over the degree of analgesia being provided thereby avoiding both breakthrough pain and overdosing. There is no reason why this mode of drug administration cannot be employed in the first opinion setting as long as facilities allow and adequate monitoring is available.

The author would only recommend the use of a constant rate opioid infusion if an infusion pump or syringe driver is available; without their use, it is very difficult to guarantee a constant rate of infusion and there are inherent risks of both under- and overdosing.

When a constant rate infusion is used, the author cannot stress enough the importance of ensuring that all calculations are double checked, clearly documented and legible to avoid confusion and potentially disastrous errors.

Morphine-lidocaine-ketamine (MLK)

The idea behind the use of this multiagent infusion is to provide multimodal analgesia with the inherent benefits that that strategy offers.

Although some institutions use standardised prepared stock solutions of morphine, lidocaine and ketamine (MLK) for convenience, the author prefers to make up the CRI solution on an individual patient basis with the initial concentrations being guided by the patient in question. Stock solutions mean that the drug concentration is fixed and the only way to adjust the doses being delivered is by adjusting the fluid rate. MLK infusions are often administered at 1-2 ml/kg/hour to start with and there is therefore relatively little scope for dose adjustment when a stock solution is used without the potential for excessive/unnecessary fluid administration as well. Moreover the doses of the individual agents being used cannot be adjusted independently.

Computerised calculators, including mobile phone applications, are increasingly available for working out how to prepare an MLK solution. In their absence, this is still relatively simple to do. An example of how to prepare an MLK solution is shown at the end of these Analgesia notes (Appendix 2).

Although the use of MLK may make sense in terms of multimodal analgesia it is important to realise that to date, to the author's knowledge, there are no clinical studies evaluating its efficacy in painful clinical patients including comparing it to other strategies. Studies published so far have evaluated effects on reducing the MAC of inhalational anaesthetics which this combination appears – unsurprisingly! – to do; however this is not the same thing as analgesic efficacy or NMDA blockade.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) in general reduce the severity of the peripheral inflammatory response and minimise peripheral sensitisation; they may also reduce central sensitisation in the spinal cord. NSAIDs may be useful in moderate to severe pain and are especially effective as synergistic analgesics with opioids in multimodal therapy.

The effects of most NSAIDs are related to the impairment of prostaglandin production; there may be other important mechanisms, some not fully understood. Prostaglandins are one of the chemical mediators that sensitise nociceptors both peripherally and centrally during 'wind up' and this anti-prostaglandin effect of NSAIDs is why they may reduce peripheral and central sensitisation. Peripheral inflammation induces central prostaglandin production hence NSAIDs may reduce central sensitisation even if the initial stimulus is peripheral.

Prostaglandin inhibition involves **cyclooxygenase (COX)** of which there are (at least) two types and the traditional dogma has been as follows:

COX-1 (constitutive, housekeeping)

- Variably found in all tissues
- Involved in the production of prostaglandins that are essential for a variety of normal functions

COX-2 (inducible)

- Levels typically very low but increase during tissue injury
- Primarily responsible for the production of prostaglandins that mediate the inflammatory response and pain associated with tissue injury

More recently it has been suggested that the traditional description above is too simplistic and that there is some overlap in the roles of COX-1 and COX-2. For example COX-2-mediated prostaglandins are thought to be vital for normal renal physiology and may also play a role in the healing of some tissues, especially the gastrointestinal tract. Some COX-1-mediated prostaglandins may be involved in the pain pathway.

Most NSAIDs are COX inhibitors. Some agents (e.g. carprofen, meloxicam) have more selective inhibition of COX-2 versus COX-1 (i.e. COX 1-sparing, 'preferentially selective') and are reportedly associated with fewer side effects and a safer therapeutic index than the older NSAIDs were. Even newer agents (e.g.

firocoxib, cimicoxib, robenacoxib) are said to be COX-2 specific inhibitors (coxibs). However there is disagreement in the literature with respect to the selectivity of different NSAIDs for COX-1 versus COX-2.

For the reason described above, it is likely that the significance of COX-1 versus COX-2 specificity in terms of the safety of an individual NSAID varies between tissues/organs depending on what role this enzyme plays in the health and healing of that tissue or organ. For example the gastrointestinal tract is highly COX-1 dependent for health so agents with greater COX-2 selectivity may be associated with fewer GI side-effects. COX-selectivity has no effect on analgesic efficacy.

In addition to their COX enzyme profile, another consideration in terms of the safety of NSAIDs is how exposed healthy non-target tissues/organs are to them. Clearly the less they are exposed, the less likely adverse effects are. In theory NSAIDs that spend less time in the circulation (have the shortest plasma half-life) and have the greatest tendency to be taken up into inflamed tissues (i.e. target sites) offer the greatest safety.

Side effects/contraindications

There is a greater potential for toxicity with NSAID use in cats because their limited ability to glucuronidate exogenous drugs results in a prolonged duration of effect with the potential for drug accumulation.

Cats seem to be particularly susceptible to the adverse renal effects of NSAIDs.

As a general point, lower doses of NSAIDs often retain all or most of the analgesic potency and a cautious approach may be rational in any cases where there is a potential concern of adverse effects.

The two most commonly recognised side effects and/or contraindications of NSAIDs use are gastroduodenal injury and renal injury.

Gastroduodenal injury

Gastroduodenal injury may occur following NSAID administration due to direct irritation of the mucosa and/or prostaglandin inhibition. Prostaglandins are important for the integrity of the gastrointestinal mucosal barrier (mucosal cytoprotection) and their impaired production therefore increases the likelihood of mucosal injury (haemorrhage, erosions, ulceration) in an already compromised tissue. Intuitively therefore NSAIDs are contraindicated in animals with gastrointestinal abnormalities.

Most serious problems reported are from administration of higher than recommended doses; but toxicity also has been reported from relatively mild doses in susceptible individuals or for example where one NSAID has been discontinued and another started without allowing for a washout period (e.g. 1 week).

However, there are patients with gastrointestinal signs in which the use of a NSAID may be justified – examples include a dog that is heavily dependent on NSAID therapy to manage discomfort associated with chronic osteoarthritis for which opioids are less effective; although it should be said that the increasing availability of tramadol may make this scenario even less likely nowadays.

Considerations in such cases include:

- Hypovolaemia or dehydration should be treated before NSAID therapy
- An agent reported to be COX-1 sparing should be chosen
- The drug should be given at a low dose and systemically if possible (mucosal lesions are more likely to occur with oral dosing because there is a higher local concentration of the agent at the site of the tablet or liquid)
- Oral administration should be accompanied by food
- Gastroprotectants (e.g. omeprazole, ranitidine) should be used pre-emptively

Renal injury

Prostaglandins play an important role in the kidneys in modulating the tone of blood vessels and regulating salt and water balance. The kidney depends on COX-1 and COX-2 for prostaglandin synthesis to autoregulate water metabolism, tubular function, and renal blood flow. Prostaglandins are not critically involved in renal haemodynamics in normal healthy animals. However, in response to a decrease in renal blood flow, locally-acting prostaglandins serve to protect renal perfusion. Their inhibition by NSAID therapy can therefore result in renal ischaemia and insufficiency. This is applicable to both older NSAIDs and newer agents with more selective COX-2 inhibition as constitutive COX-2 is produced in the kidney. Emergency patients in whom renal blood flow may be decreased include those with hypovolaemia, cardiac insufficiency and pre-existing renal disease.

NSAID administration to patients in volume deplete states (e.g. hypovolaemic shock post-trauma) poses a real risk of nephrotoxicity, acute kidney injury and possibly failure.

Other side-effects/considerations of NSAIDs

- Any NSAID has the potential to cause hepatic injury which may be intrinsic (predictable and dose-related; e.g. acetaminophen, aspirin) or idiosyncratic (unpredictable, non-dose related – this applies to most other NSAIDs).
    - Administration of NSAIDs to animals that have hepatic disease has been questioned because of the role of the liver in metabolising these drugs, and they should probably be used cautiously if at all with active liver disease.
    - There is no evidence that prior hepatic disease predisposes a patient to NSAID-induced liver injury. Drug enzyme systems are remarkably well preserved in hepatic disease and pre-existing hepatic disease is not necessarily a contraindication for NSAID administration.
- Interference with coagulation
- NSAIDs should not be administered concurrently with corticosteroids

Hypovolaemia/dehydration

The use of NSAIDs is contraindicated in patients with hypovolaemia, hypoperfusion from other causes, or dehydration.

A large proportion of painful emergency patients fall into this category and NSAIDs should not be used in the initial management of such cases. Depending on the primary disorder, it *may* be appropriate to administer a NSAID following correction of hypoperfusion and dehydration, for example 12-48 hours following initial presentation, as long as the patient is stable and there are no other contraindications.

Important information that should guide treatment:

- "All NSAIDs, regardless of COX-1/COX-2 specificity, are capable of producing gastrointestinal lesions, particularly at high doses.
- All NSAIDs (selective or non-selective) can produce other gastrointestinal signs, including vomiting, diarrhoea, and decreased appetite, without producing ulceration.
- All NSAIDs have potential for producing hepatic injury. Susceptibility seems to be [largely] idiosyncratic and unpredictable.
- All NSAIDs have the potential for producing renal injury. Previous renal disease, salt depletion, [hypovolaemia] and dehydration increase the risk.
- No NSAID is consistently more clinically effective than another."

(Papich MG. An Update on Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Small Animals. Vet Clin Small Anim 2008. 38:1243-1266.)

Plus…there are currently no studies that have shown one NSAID to be a better analgesic than another; and given they have similar adverse effect profiles, other considerations such as palatability, licensed routes and costs may affect which agent is chosen.

Paracetamol (acetaminophen)

Paracetamol (acetaminophen) is not commonly used therapeutically in veterinary medicine due to the widespread availability of licensed veterinary products that are both more effective and have been subjected to extensive clinical trials. However it may be an underused treatment option and is gaining more traction especially in referral centres both for treating fever and pain. Paracetamol is also widely available from numerous outlets and frequently present within the home of many pet carers. It is therefore common in emergency practice to either receive enquiries about administering paracetamol to dogs or to see animals to which this agent has been administered.

Paracetamol may be a useful analgesic in dogs but **it should never be administered to cats** at any dose due to the reduced capacity for glucuronidation in this species and therefore significantly increased risk of toxicity.

Paracetamol is a NSAID and interferes with prostaglandin synthesis, but it is unclear whether COX inhibition is involved and/or the only mechanism of action. It is analgesic but not anti-inflammatory at clinical doses; it also has antipyretic activity. However it is not associated with either renal or gastrointestinal injury at clinical doses. Paracetamol can therefore be used either in addition to conventional NSAIDs or alone in dogs in which these agents are contraindicated or poorly tolerated. As paracetamol interferes with prostaglandin production, it should be avoided in hypoperfused or dehydrated patients.

Hepatotoxicity is a potential side effect of this drug but it has a high safety index in dogs.

The recommended dose range in dogs is 10-15 mg/kg p.o. q 8-12 hours.

A combined preparation of paracetamol and codeine is commercially available for dogs but the author has no experience with its use.

Local anaesthetic agents

Local anaesthetic agents work by blocking sensory input via afferent nerve fibres to the central nervous system and prevent central sensitisation. Longer-acting agents in particular (e.g. bupivacaine, ropivacaine) are used extensively in referral centres in a number of ways including:

- Epidural administration (often combined with morphine)
- Intrapleural administration via thoracostomy tubes following thoracotomy
- Local and regional nerve blocks
- Constant rate infusion of 2% lidocaine solution without adrenaline for analgesic purposes in dogs:
    - There are some studies showing efficacy of this route in dogs (and humans)
    - Traditionally it has been said that lidocaine infusion may result in significant cardiovascular depression in cats and is not recommended unless essential for controlling ventricular dysrhythmia. The evidence base for this is minimal however and to the author's knowledge is all based on the haemodynamic effects of lidocaine infusion in healthy cats under general anaesthesia. Some clinicians have used lidocaine infusion for analgesia purposes in cats for some time without noting more adverse effects than in dogs. Nevertheless until and unless the recommendation not to use lidocaine infusions in cats for analgesia changes generally, it is probably best to avoid this practice.
    - The analgesic mechanism of action when administered intravenously is not known but may involve both peripheral and central sites of action; systemic lidocaine may block propagation of ectopic discharge from the site of neuronal injury as well as within the dorsal root ganglion.

While these uses may not be applicable to most non-referral emergency patients, local anaesthetic agents can be employed to good effect in this setting. Local and regional anaesthesia is underused probably due to a combination of lack of training for small animal (versus equine) vets but also because it is overlooked because many of our patients undergoing procedures receive full general anaesthesia. However physiological principles mean that there is still a benefit from using local anaesthesia regardless of general anaesthesia as part of a multimodal approach to block the nociceptive impulses close to their source. Furthermore this may have a dose-sparing effect on the general anaesthetic agents.

"Regional anaesthesia always works – provided you put the right dose of the right drug in the right place" (British Journal of Anaesthesia, Denny and Harrop-Griffiths 2005).

Lidocaine

Lidocaine has a shorter duration of action (1-2 hours) than other agents but a rapid onset of action (can be as quick as 3-5 minutes). It is the most widely available local anaesthetic agent and may be used for emergency cases in a number of ways. Examples include:

1. **Topical analgesia for wounds**:
   - While an emergency patient is undergoing initial stabilisation, sterile gauze swabs can be soaked in a solution of 2% lidocaine mixed with normal saline (0.9% sodium chloride) and applied to wounds which are then wrapped in cling film pending management at the appropriate time. Lidocaine can also be mixed with the gel that is applied to the wound prior to clipping.
   - Maximum recommended dose is 12 mg/kg in dogs [6 mg/kg in cats]
   - A 5% lidocaine patch (Lidoderm®, Endo Pharmaceuticals) is available and has been used for dogs (and cats) with severe skin abrasions, severe bruising and surgical wounds. However the author has no experience with its use.
   - There is also experience with the use of lidocaine putty in human medicine.

2. **EMLA® cream 5%** (AstraZeneca); contains 2.5% lidocaine and 2.5% prilocaine:
   - Can be applied to the skin prior to intravenous catheter placement or venepuncture.
   - Depending on the site, a light occlusive dressing may be appropriate while anaesthesia takes effect.
   - EMLA® cream is especially useful for example in puppies (and kittens, rabbits etc.) and in stressed animals.
   - EMLA® cream can also be applied to wound edges to reduce irritation and thereby patient interference.
   - Clinical experience suggests that onset of action in some cases is significantly shorter than the commonly reported 30-60 minutes.
   - It may be that unless you wait for at least 30 minutes, the desensitisation achieved will not be as full as possible. However clinical experience does suggest that the effect is sufficient in less than 30 minutes (even if this is just due to a soothing placebo effect of the cream preparation!).
   - Minimal if any systemic drug absorption has been reported following topical application.

3. **Lidocaine spray**: in addition to facilitating endotracheal intubation of cats, proprietary lidocaine spray (e.g. Intubeaze®, Dechra Veterinary Products) may have diverse uses for mucosal desensitisation, for example to facilitate nasal catheter placement or to examine the oropharyngeal region. Some people have also used Intubeaze® on clipped skin prior to venepuncture/catheterisation in lieu of EMLA® cream, and also for minor stitch-ups/stapling procedures, although there is debate about how well and quickly this preparation would be absorbed through the skin to achieve nerve anaesthesia (it lacks the 'vehicle' in the EMLA® cream base that is meant to allow effective absorption across the skin).

4. **Lidocaine lubricant**: a 2% lidocaine lubricant is commercially available; otherwise it can be constituted by mixing 2% lidocaine solution (without adrenaline) for injection with a sterile lubricant. This is then used topically, for example prior to insertion of nasal catheters or urinary catheterisation.

Solutions of other local anaesthetics (e.g. tetracaine hydrochloride, proxymetacaine) have also been used topically to facilitate conscious small stitch-ups or 'staple-ups' although the same comments about how effectively they are absorbed across the skin apply to those under 'Lidocaine spray' above.

Ketamine

There are said to be four stages of ketamine brain continuum – analgesia, sedation, partial dissociation, dissociation; they have overlapping dose ranges that can vary between patients. Ketamine has been used mostly as a dissociative anaesthetic agent or sedative but it also has a role in pain relief. This is predominantly an anti-hyperalgesia and anti-allodynic preventative analgesic effect by blocking (and potentially reversing) central sensitisation via its action as an N-methyl-D-aspartate (NMDA) receptor antagonist; the NMDA receptor is a key receptor in the dorsal horn of the spinal cord. It is especially effective in this respect when combined with a full opioid agonist and may be used as a constant rate infusion.

The recommended dose for analgesic purposes is 0.1-1 mg/kg i.v. as needed (often every 30 minutes) or a single loading dose followed by a constant rate infusion of 0.1-1 mg/kg/hour. Following a single bolus, ketamine's effect on blocking central sensitisation likely persists for much longer than the direct analgesic effect. Ketamine is sympathomimetic and may therefore cause increases in heart rate and blood pressure; it is relatively contraindicated therefore for example in cats with hypertrophic cardiomyopathy. Ketamine was previously said to be contraindicated in raised intracranial pressure (e.g. after head trauma) but this is no longer considered the case.

It should NOT be used alone, especially in dogs, as severe hyperexcitability/mania/other horrible behavioural effects may ensure!

FND OUT MUCH MORE ABOUT KETAMINE ON THIS FREE PODCAST EPISODE:
http://www.veteccsmalltalk.com/episode/14

Medetomidine

Medetomidine is an alpha$_2$-adrenergic agonist that is used most commonly for its sedative properties. This agent does however also possess potent analgesic properties, acting at similar sites in the central nervous system as opioids as well as at primary afferent fibres, and can be a useful adjunctive analgesic in some cases.

At the microdoses recommended here, cardiovascular (marked peripheral vasoconstriction, vagal baroreceptors-mediated bradycardia, decreased cardiac output) and respiratory (depression) effects seen should be minimal and can be reversed by atipamezole if necessary. The sedative effects are likely to be advantageous for patient management in the types of cases in which this agent may be employed as an analgesic.

Recommended doses for medetomidine when used for analgesic purposes are 1-5 μg/kg slow i.v. or i.m. as needed (often q 30-90 minutes but potentially much longer if an opioid is used concurrently); alternatively a constant rate infusion of 1-3 μg/kg/hour may be used and is likely more effective; an

initial loading dose of 1-5 μg/kg is usually given. NB. The above comments also apply to **dexmedetomidine** although lower doses are typically used.

Alpha$_2$-adrenergic agonists can be given via the oral transmucosal/buccal route in fractious cats.

Non-Pharmacological Measures

Although analgesic agents are the mainstay of pain management, it is essential not to overlook the important contribution of good nursing care and other non-pharmacological measures. These measures reduce stress, improve patient wellbeing, and contribute significantly to pain management. Some of these measures are listed below:

- TLC, gentle handling (independent of interventions) and regular grooming
- Providing a suitable environment (some animals prefer a dimly lit quiet environment, others like to be distracted)
- Tempting to eat if appropriate
- Ensuring bedding is dry, clean and comfortable
- Providing a familiar blanket or toy from home
- Allowing or preventing visits by the owner depending on patient response
- [Providing cats with a box or carrier to sleep in]
- Helping dogs out to urinate/defaecate
- Bladder management as necessary
- Co-ordinating interventions (e.g. venepuncture) to minimise the number of painful procedures performed
- Grouping treatments to allow undisturbed rest time
- Removing unnecessary catheters, tubing and bandages as soon as possible
- Using warm compresses or cold packs if appropriate
- Outside for fresh air and hopefully some sunshine!

External stabilisation of orthopaedic injuries may offer considerable pain relief and reduce the likelihood of further patient-induced damage.

Cats are more sensitive and more susceptible to stress than dogs, and the importance of non-pharmacological measures cannot be overstated in this species.

Appendix 1 Pain Scales

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ **Date** / / **Time**

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog? *(v)*		*Is the dog?* *(vi)*	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

Total Score (i+ii+iii+iv+v+vi) = _____

The analgesia protocol should be adjusted if total score > 5 (if section B not performed); total score > 7; or you think the patient is uncomfortable regardless of the score!

This version is available online:
(http://www.gla.ac.uk/schools/vet/research/painandwelfare/downloadacutepainquestionnaire/)

Can be downloaded at Colorado State University website

Colorado State University

Date _____

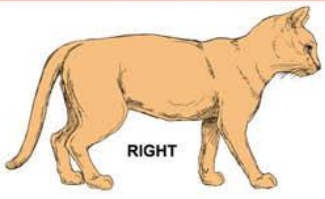
Time _____

Colorado State University Veterinary Medical Center

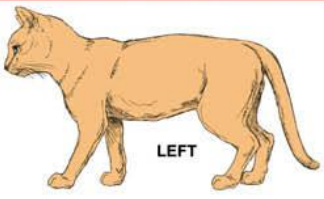
Feline Acute Pain Scale

Rescore when awake
- ☐ **Animal is sleeping, but can be aroused - Not evaluated for pain**
- ☐ **Animal can't be aroused, check vital signs, assess therapy**

Pain Score	Example	Psychological & Behavioral	Response to Palpation	Body Tension
0		☐ **Content and quiet** when unattended ☐ **Comfortable** when resting ☐ Interested in or **curious** about surroundings	☐ **Not bothered** by palpation of wound or surgery site, or to palpation elsewhere	Minimal
1		☐ **Signs are often subtle and not easily detected in the hospital setting**; more likely to be detected by the owner(s) at home ☐ Earliest signs at home may be **withdrawal from surroundings or change in normal routine** ☐ In the hospital, may be content or slightly unsettled ☐ **Less interested** in surroundings but will look around to see what is going on	☐ May or may not react to palpation of wound or surgery site	Mild
2		☐ Decreased responsiveness, **seeks solitude** ☐ **Quiet**, loss of brightness in eyes ☐ **Lays curled up or sits tucked up** (all four feet under body, shoulders hunched, head held slightly lower than shoulders, tail curled tightly around body) with eyes partially or mostly closed ☐ **Hair coat appears rough** or fluffed up ☐ May intensively groom an area that is painful or irritating ☐ Decreased appetite, **not interested in food**	☐ **Responds aggressively or tries to escape** if painful area is palpated or approached ☐ Tolerates attention, may even perk up when petted as long as painful area is avoided	Mild to Moderate **Reassess analgesic plan**
3		☐ Constantly **yowling, growling, or hissing** when unattended ☐ May bite or chew at wound, but **unlikely to move** if left alone	☐ **Growls or hisses at non-painful palpation** (may be experiencing allodynia, wind-up, or fearful that pain could be made worse) ☐ **Reacts aggressively** to palpation, **adamantly pulls away** to avoid any contact	Moderate **Reassess analgesic plan**
4		☐ Prostrate ☐ Potentially **unresponsive** to or unaware of surroundings, difficult to distract from pain ☐ Receptive to care (even mean or wild cats will be more tolerant of contact)	☐ **May not respond** to palpation ☐ **May be rigid to avoid painful movement**	Moderate to Severe **May be rigid to avoid painful movement** **Reassess analgesic plan**



○ Tender to palpation
× Warm
■ Tense



Comments _____

REVISED GLASGOW COMPOSITE MEASURE PAIN SCALE FOR ACUTE PAIN IN CATS: CMPS – FELINE

Choose the most appropriate expression from each section and total the scores to calculate the pain score for the cat, if more than one expression applies choose the higher score

LOOK AT THE CAT IN ITS CAGE

Question 1

Is it?

Silent / purring / meowing	0
Crying/growling / groaning	1

Question 2

Relaxed	0
Licking lips	1
Restless/cowering at back of cage	2
Tense/crouched	3
Rigid/hunched	4

Question 3

Ignoring any wound or painful area	0
Attention to wound	1

APPROACH THE CAGE, CALL THE CAT BY NAME & STROKE ALONG ITS BACK FROM HEAD TO TAIL

Question 4

Does it?

Respond to stroking	0

Is it?

Unresponsive	1
Aggressive	2

IF IT HAS A WOUND OR PAINFUL AREA, APPLY GENTLE PRESSURE 5 CM AROUND THE SITE. IN THE ABSENCE OF ANY PAINFUL AREA APPLY SIMILAR PRESSURE AROUDN THE HIND LEG ABOVE THE WOUND

Question 5

Does it?

Do nothing	0
Swish tail/flatten ears	1
Cry/hiss	2

Growl	3
Bite/lash out	4

Question 6

General impression

Is the cat?

Happy and content	0
Disinterested/quiet	1
Anxious/fearful	2
Dull	3
Depressed/grumpy	4

Pain Score …/ 16

Administer analgesia if pain score ≥4.

From Calvo G, Holden E, Reid J, et al. Development of a behaviour-based measurement tool with defined intervention level for assessing acute pain in cats. J Sm Anim Pract 2014. 55(12):622-629.

Appendix 2 MLK Calculation

Example of preparation of a morphine, lidocaine and ketamine (MLK) solution for constant rate infusion:

Patient's name:
Patient's body weight: 20 kg
Initial infusion rate: 1 ml/kg/h = 20 ml/h

1. Select initial dose rates for analgesic agents:

Drug: **morphine** (10 mg/ml)
Initial dose rate: 0.2 mg/kg/h = 4 mg/h

Drug: **lidocaine** (20 mg/ml i.e. 2%)
Initial dose rate: 50 µg/kg/min = 1000 µg/min = 1 mg/min = 60 mg/h

Drug: **ketamine** (100 mg/ml)
Initial dose rate: 0.5 mg/kg/h = 10 mg/h

2. Select volume of crystalloid (normal saline or Hartmann's) to be used and calculate how long this volume will last for:

Volume of crystalloid to be used: 500 ml bag ∴ 500 ml bag will last for 25 h (i.e. 500 ml divided by 20 ml/h)

3. Calculate volume of analgesic agents required for this period of time, i.e. in this example 25 h:

Morphine: 4 mg/h x 25 h = 100 mg = 10 ml (i.e. 100 mg divided by 10 mg/ml solution)
Lidocaine: 60 mg/h x 25 h = 1500 mg = 75 ml (i.e. 1500 mg divided by 20 mg/ml solution)
Ketamine: 10 mg/h x 25 h = 250 mg = 2.5 ml (i.e. 250 mg divided by 100 mg/ml solution)

4. Remove a volume of crystalloid from the bag that is equal to the total volume of analgesic agents to be added, i.e. in this example 10 + 75 + 2.5 = 87.5 ml

5. Add analgesic agents to the crystalloid solution

6. Label the MLK solution for infusion clearly with drug concentrations, date, time, name of person preparing the solution, and name of person double checking preparation

Note: it is extremely important to ensure that two individuals check all of the above calculations and all of the volumes of analgesic agents and crystalloid removed/added. This safeguard will hopefully prevent potentially serious errors from occurring.