DKA: keeping calm and carrying on

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IDEXX

Disclosure

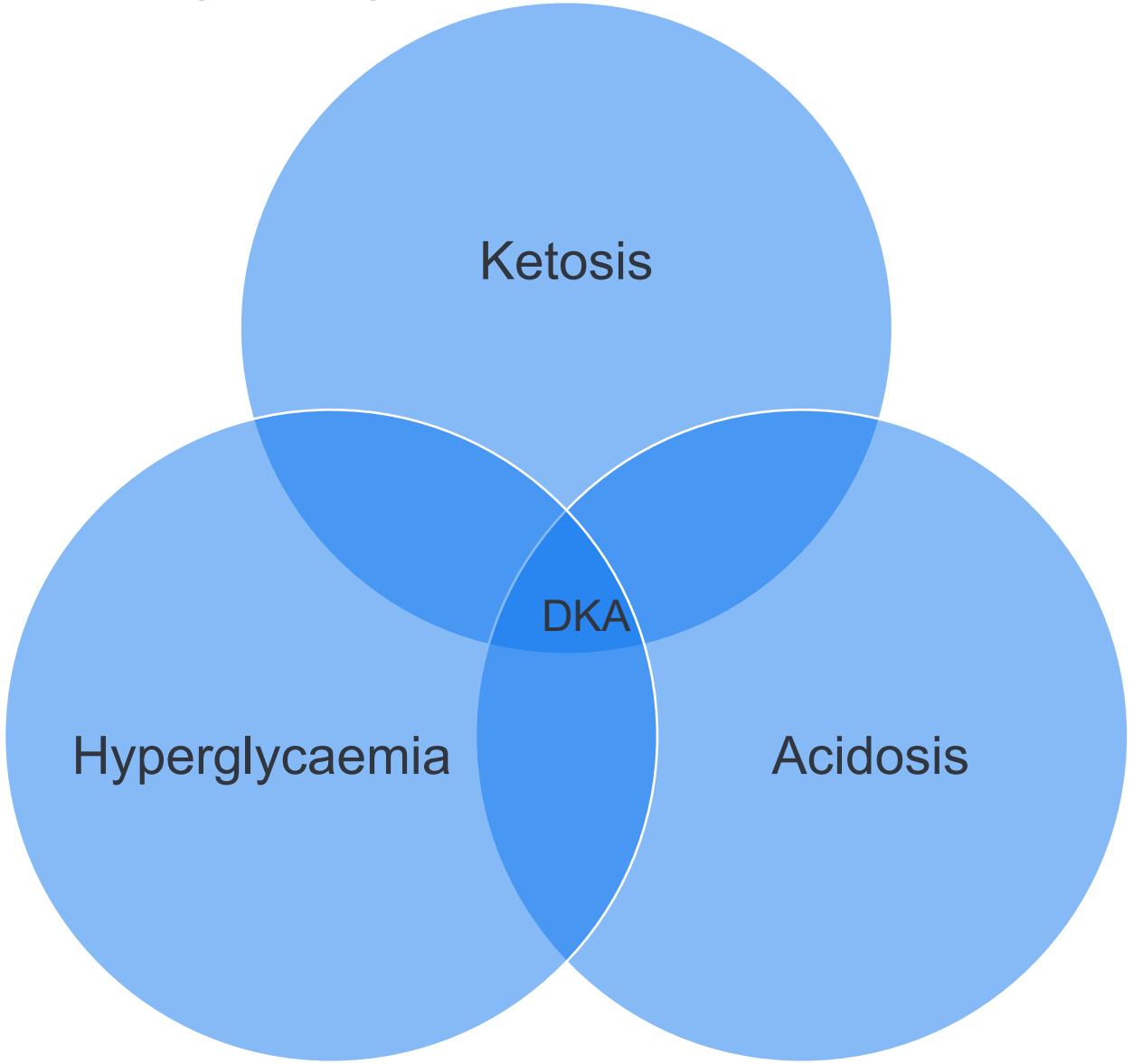
- IDEXX Employee

The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation, and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions, and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.

Agenda

1. Pathophysiology
2. Presentation
3. Diagnostics
4. Treatment
5. Case Studies
6. Q&A

Diabetic ketoacidosis (DKA)



Euglycaemic diabetic ketoacidosis

- Seen with SGLT2 inhibitors
  - Prevents glucose reabsorption
    - Causes excess blood glucose to be renally excreted
- DKA can be seen at any time but especially within first 2 weeks
- Typical DKA may occur but can also see DKA without hyperglycaemia
  - Insulin protocols still required but may need supplement glucose at an earlier stage

Ketones

- Used as an energy source during period of glucose deficiency
- In uncomplicated diabetes production occurs slowly
- A lack of insulin results in increased activity of Hormone Sensitive Lipase
  - Increases release of Free Fatty Acids from the adipocytes.
  - Reduced utilisation of both glucose and ketones.
- Concurrent illness increases counter regulatory hormones and promotes further insulin resistance
- Overall, this leads to an increase in glucose and ketones in the bloodstream and DKA can result.

Effect of insulin deficiency

Reduced glucose uptake/increased gluconeogenesis

Increased Protein Catabolism

Increased lipid catabolism

DKA

- DKA is usually the result of concurrent disease which results in increased glucagon:insulin ratio.

- In uncomplicated diabetes production of ketones usually occurs slowly and as such ketones can be used by peripheral tissues for energy and not result in DKA.

Presentation

- DKA can occur as first sign of DM or can occur as a result of previously diagnosed and uncontrolled DM
- Clinical signs variable but often include anorexia, lethargy and dehydration and/or weakness or collapse
- Ketones can be identified in plasma or urine

Ketones

- Nitroprusside reaction in dipsticks used to detect ketones
  - Can be detected in urine or plasma
- Test detects acetone & acetoacetate but NOT beta hydroxybutyrate
- Insulin therapy will result in metabolism of beta hydroxybutyrate to acetoacetate
- Can initially be negative
- Test may continue to be positive despite clinical improvement

Ketones

- Ketometer measures beta hydroxybutyrate
- Beta hydroxybutyrate main ketone in DKA and it is metabolised to acetoacetate
- Ketometer therefore can be more accurate at detecting DKA than dipsticks

Dipstick ketone measurements

- Previous study compare the results of urine and plasma ketone dip test in a group of diabetic cats with possible ketosis or ketoacidosis, using laboratory plasma beta-hydroxybutyrate measurements as the gold standard
- The best cut-off value to detect cats with ketoacidosis was 1.5 mmol/l for urine and 4 mmol/l for plasma.
- The sensitivity/specificity was 82/95 per cent for urine and 100/88 per cent for plasma, respectively.

Zeugswetter F, Pagitz M. Ketone measurements using dipstick methodology in cats with diabetes mellitus. J Small Anim Pract. 2009 Jan;50(1):4-8. doi: 10.1111/j.1748-5827.2008.00657.x. Epub 2008 Nov 13. PMID: 19037889.

Ketometer

- Previous study to evaluate accuracy and precision of a hand-held ketone meter measuring β-hydroxybutyrate and to determine its diagnostic performance to rule out ketoacidaemia in diabetic cats.
- A β-hydroxybutyrate concentration of >2·55 mmol/L had a sensitivity of 94% and a specificity of 68% for diagnosing ketoacidaemia.
- Concentration <2·55 mmol/L enable ketoacidaemia to be excluded and should lead to redirection of differential diagnoses.

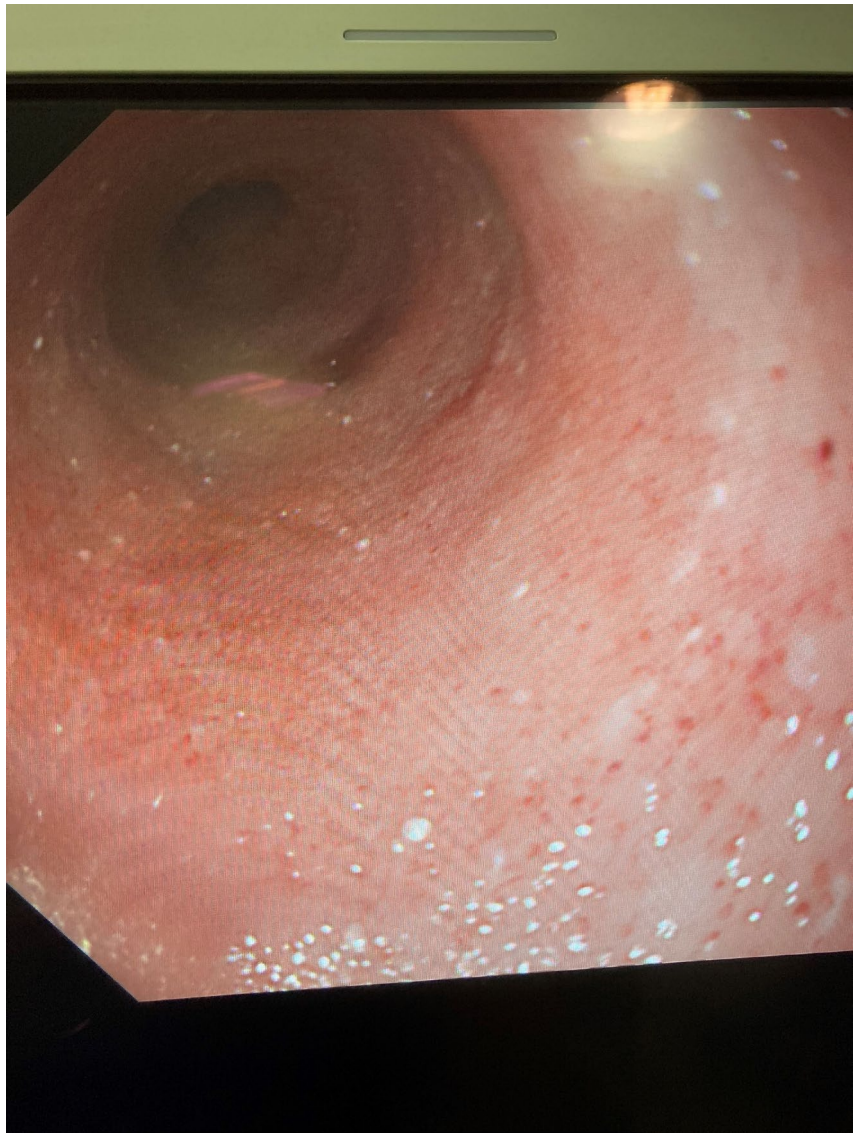
Zeugswetter FK, Rebuzzi L. Point-of-care β-hydroxybutyrate measurement for the diagnosis of feline diabetic ketoacidaemia. J Small Anim Pract. 2012 Jun;53(6):328-31. doi: 10.1111/j.1748-5827.2012.01204.x. Epub 2012 Apr 26. PMID: 22533366.

Clinical signs

+ Weakness or collapse
+ PU/PD
+ Anorexia
+ Vomiting
+ Diarrhoea
+ Acetone smell
+ Tachypnoea

Common concurrent disease

+ Pancreatitis
+ Infections, particularly UTI
+ Gastrointestinal disease
+ Neoplasia
+ Hepatic lipidosis in cats



Dehydration & electrolyte abnormalities

- Predominant feature in DKA.
  - Osmotic diuresis
  - Fluid loss due to vomiting and/or diarrhoea
  - Anionic charge on the ketones results in excretion of positively charged ions
    - sodium, potassium, calcium and magnesium
  - Insulin required for tubular reabsorption of sodium, chloride, potassium and phosphorus

Fluid therapy

- Primary aim is to replace the fluid and electrolyte deficits
- Patients have a high fluid requirement due to poorly controlled DM +/- losses as a result of vomiting/diarrhoea.
- 0.9% saline or compound sodium lactate
- Important to bolus first if hypotensive and then rehydration can begin.

Calculation of fluid rates

- Initially boluses are required to normalise blood pressure
- Rehydration therapy can then begin
- For rehydration need to consider 3 different components:
  - Replacement of hydration losses
    - Deficit (ml) = Body weight (Kg) x % dehydration x 10
  - Maintenance requirements
    - Estimated at 60ml/kg/day
  - Ongoing losses
    - Estimated based on volume of vomitus/diarrhoea etc

Potassium Supplementation

+ May be hyperkalaemic on presentation due to dehydration
+ Lack of insulin means that the influx of potassium is reduced
+ Intracellular potassium measurement underestimated
+ Insulin therapy will cause translocation of potassium from the extracellular compartment into the cells

Potassium Supplementation in DKA

Serum Potassium (mmol/L)	Potassium (mmol) added to 1L of fluid
>5.5	None initially
4.1-5.4	20
3.1-4	30
2.6-3	40
<2.5	60-80

Max rate 0.5mmol/kg/hr

Adapted with permission from Skelly, BJ. Endocrine emergencies. From: BSAVA Manual of Canine and Feline Emergency and Critical Care, 3rd edition. © BSAVA

Phosphate

- Hypophosphatemia occurs due to osmotic diuresis and reduced renal tubular absorption
- Insulin therapy will cause translocation of phosphate from the extracellular compartment into the cells
- Potassium phosphate used to supplement
- Treatment indicated if <1.5mg/dL
- Clinical signs are rare however haemolytic anaemia has been reported in cats
- CRI at 0.01-0.06mmol/kg/hr

Bicarbonate

- Very rarely required
- IVFT and Insulin therapy alone will reduce acidosis
- If the acidosis is severe; pH <7, or plasma bicarbonate <8mEq/L then bicarbonate can be considered
- Bicarbonate therapy however should NOT be administered if it is not possible to measure blood gases

Bicarbonate

- The bicarbonate deficits in mEq can be estimate as below:
  - 0.3 x BW (Kg) x (24-bicarbonate)
- Generally ¼ to ½ of the dose is administered slowly after 2-4 hours and then blood gases are repeated and additional bicarbonate given as required

Insulin therapy

- Usually delayed for at least 2 hours after fluid therapy has been started
- Fluid therapy alone will help to reduce the serum glucose concentration
- Insulin is usually supplemented IV or IM intramuscularly using soluble/regular insulin.

CRI neutral insulin protocol

- Add 1.1-2.2IU/Kg Neutral insulin to 250ml of 0.9% saline or Hartmann's
  - Provides 0.05-0.1U/kg/hr insulin infusion
- Invert bag and ensure it has been mixed well
- Insulin should be protected from the light and 30-50ml of the resultant solution should be run through the line to attain stable solution

CRI neutral insulin protocol

- BG measured q1-2hr
- Aim to keep BG at 8-15mmol/L
- If BG <11mmol/L then add glucose to fluids and insulin CRI is reduced by 50%
- Rest of the fluid requirements + K supplementation added to a separate bag.

CRI neutral insulin protocol

Blood glucose in mmol/l	Dextrose added to fluid	Insulin CRI in ml/hr
>17	None	10
11-17	None	7
5.5-11	2.5%	5
<5.5	5%	0

Making up dextrose CRI

- Use 50% dextrose.
- To make a 5% dextrose solution remove 50ml of Hartmann's and replace with 50ml of dextrose and shake well.
- To make a 2.5% dextrose solution remove 25ml of Hartmann's and replace with 25ml of dextrose and shake well.

IM neutral insulin protocol

+ Administer 0.2IU/kg IM neutral insulin
+ BG measured q1-2hr
+ Aim to keep BG at 8-15mmol/L
+ Repeat IM neutral insulin at 0.1IU/kg q hr
+ If BG <8mmol/L then add 5% glucose to fluids and try to continue insulin therapy

Feline IM glargine +/- SQ glargine protocol

- Based on a 2013 study by Marshall et al (1)
- Started with 1-2IU IM of glargine initially
- Most cats then received 1-3IU of SQ glargine
- Followed by intermittent IM glargine (0.5-1IU) q2 -22 hours and (1-2IU) SQ glargine q12hr
- BG was assessed q2-4hr with aim to lower BG by 2-3mmol/L/hr until 10-14mmol/L.
- Repeated 0.5-1 IU IM as required (2-22hr)

(1) Marshall RD, Rand JS, Gunew MN, Menrath VH. Intramuscular glargine with or without concurrent subcutaneous administration for treatment of feline diabetic ketoacidosis. J Vet Emerg Crit Care (San Antonio). 2013 May-Jun;23(3):286-90. doi: 10.1111/vec.12038. Epub 2013 Mar 26. PMID: 23530935.

Feline IM glargine +/- SQ glargine protocol

- IV glucose administered if BG <10mmol/L
  - Glucose bolus over 5 min
  - Then CRI of 2.5% glucose
- If restricted finances, then no or conservative evening dose of insulin and glucose supplemented IV fluids.
- All cats survived to discharge and 87% still alive after median follow up of 1.9 years
- 1/3 of cats subsequently achieved remission

Lispro

Journal of Feline Medicine and Surgery
Volume 21, Issue 2, February 2019, Pages 115-123

https://doi.org/10.1177/1098612X18761696

Original Article

Use of lispro insulin for treatment of diabetic ketoacidosis in cats

Eleonora Malerba, Michela Mazzarino, Francesca Del Baldo, Sara Corradini, Gaia Carotenuto, Massimo Giunti, and Federico Fracassi

ORIGINAL RESEARCH article

Front. Vet. Sci., 16 October 2020
Sec. Veterinary Emergency and Critical Care Medicine
Volume 7 - 2020 | https://doi.org/10.3389/fvets.2020.559008

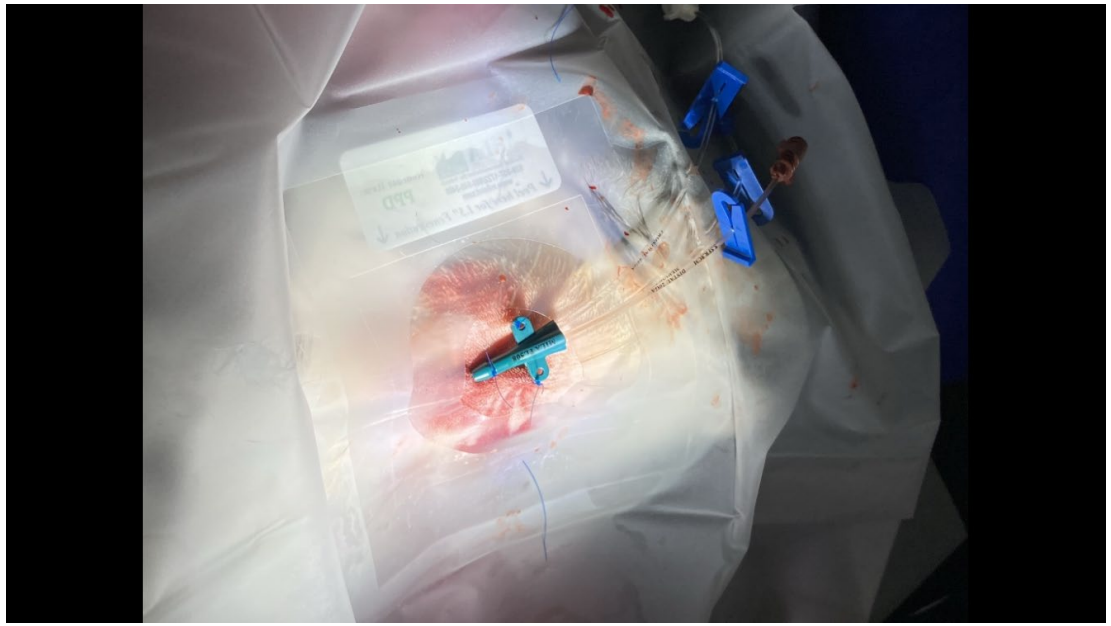
Efficacy and Safety of Intramuscular Insulin Lispro vs. Continuous Intravenous Regular Insulin for the Treatment of Dogs With Diabetic Ketoacidosis

Eleonora Malerba, Federica Alessandrini, Giorgio Grossi, Massimo Giunti and Federico Fracassi*

Department of Veterinary Medical Sciences, University of Bologna, Bologna, Italy

Monitoring

- BG should be checked every 1-2hours
- Electrolytes esp. K+ should be checked every 4-6hr initially
- Once DKA has resolved and the patient is eating then traditional SQ insulin can be started



Assessing for underlying disease

- Urinalysis
- Full blood work +/- folate, cobalamin and feline pancreatic lipase immunoreactivity (fPLI)
- Thoracic radiographs and abdominal ultrasound as indicated

Nutrition

- It is important to try and tempt patients to eat as soon as possible.
- Once they are eating normally then their usual SQ insulin can be restarted.
- In some cases parenteral feeding may be required either by placing a nasogastric tube or oesophageal feeding tube.
- Additional supportive care such as maropitant and mirtazapine may also be required.

Transitioning to SQ insulin

+ Once fully hydrated
+ Once eating well

Smudge

- 12yr DSH
- Multicat household and has outdoor access
- PU/PD reported by owner over previous month
- Over past month dramatic weight loss
- This morning very depressed, inappetance and episodes of bilious vomiting

Physical examination

+ Poor body condition, BW 4.1Kg
+ Dull and depressed
+ Hypothermic at 36.7°C
+ HR 130, very poor peripheral pulses
+ MM pale and tacky
+ RR 40
+ Thoracic auscultation and abdominal palpation unremarkable
+ Systolic blood pressure 60mmHg

Emergency database

+ PCV 38%
+ TS 90g/L
+ Glucose 34mmol/L
+ pH 7.2

Initial fluid resuscitation

- 5ml/kg bolus Hartmann's over 10minutes and then reassessed
  - Systolic blood pressure 65mmHg, HR 140, poor pulses
- Repeat 5ml/kg/hr bolus
  - Systolic blood pressure 75mmHg, HR 160, poor pulses
- Repeat 5ml/kg/hr bolus
  - Systolic blood pressure 90mmHg HR 160, fair pulses
- Repeat 5ml/kg/hr bolus
  - Systolic blood pressure 105mmHg HR 168, fair pulses

Stabilisation

- Started active warming with heated bed
- Addressed dehydration
  - Replacement of hydration losses
    - Deficit (ml) = Body weight (Kg) x % dehydration x 10
      - = 4.1 x 10 x 10 = 410ml
  - Maintenance requirements
    - Estimated at 60ml/kg/day
    - =246ml
  - Ongoing losses
    - Estimated based on volume of vomitus/diarrhoea etc
    - 3 x 10ml = 30ml
    - Total = 686ml/day =28ml/hr

Glucose	**28.2**	3.9 - 8.0 mmol/L
IDEXX SDMA	9	1 - 14 µg/dL
Creatinine	146.0	80.0 - 203.0 µmol/L
Urea	**27.1**	2.5 - 9.9 mmol/L
Phosphorus	1.95	0.90 - 2.20 mmol/L
Sodium	**144.3**	145.0 - 157.0 mmol/L
Potassium	**3.33**	3.50 - 5.50 mmol/L
Na: K Ratio	**43.33**	28.00 - 40.00
Chloride	108.7	100.0 - 124.0 mmol/L
Total Protein	**86.4**	60.0 - 80.0 g/L
Albumin	39.3	25.0 - 45.0 g/L
Globulin	**47.1**	25.0 - 45.0 g/L
Albumin: Globulin Ratio	0.83	0.60 - 1.50

ALT	117.2	5.0 - 60.0 U/L	
Amylase	1,685.4	100.0 - 1,200.0 U/L	
Lipase	21.3	<= 89.0 U/L	
Fructosamine	a. 682	137 - 286 µmol/L	
Total T4	a. 30	10 - 60 nmol/L	

Urinalysis

	Urine Appearance	CLEAR
	Colour	YELLOW
	Specific Gravity	1.022
	pH	5.0
	Urine Protein	+
	Glucose	++++
	Ketones	+++
	Blood / Haemoglobin	NEGATIVE
	Bilirubin	NEGATIVE

	White Blood Cells	None seen	
	Red Blood Cells	<5	/hpf (<5)
	Epithelial Cells	None seen	
	Casts	None seen	
	Crystals	None seen	

Urine Culture		No bacterial growth.
Urine Antibacterial Activity	a	NEGATIVE

When to start insulin

- Previous study to determine whether early insulin administration (≤6 h after admission) results in more rapid resolution of diabetic ketosis (DK) and ketoacidosis (DKA), shorter duration of hospitalization, and higher incidence of complications, and whether more severe ketonuria is associated with longer time to resolution of DK/DKA.
- Early group patients had more rapid resolution of DK/DKA after starting short-acting insulin therapy
- There was no difference in duration of hospitalization or complications.

DiFazio J, Fletcher DJ. Retrospective comparison of early- versus late-insulin therapy regarding effect on time to resolution of diabetic ketosis and ketoacidosis in dogs and cats: 60 cases (2003-2013). J Vet Emerg Crit Care (San Antonio). 2016 Jan-Feb;26(1):108-15. doi: 10.1111/vec.12415. Epub 2015 Nov 9. PMID: 26551019.

Insulin CRI

+ BG 28.2mmol/L
+ Added 1.1IU/Kg Neutral insulin to 250ml of 0.9% saline
+ Started insulin CRI at 10ml/hr
+ Hartmann's + KCL given at 18ml/hr

Investigations

+ Haematology/serum biochemistry
+ fPLI
+ Urinalysis
+ Thoracic radiographs
+ Abdominal ultrasound

NO UNDERLYING CAUSE IDENTIFIED

Management and outcome

- Continued on neutral insulin for 3 days
- Began eating consistently and transitioned to SQ Prozinc BID
- Transitioned to diabetic diet
- Stabilised well after a couple months

Princess

- 10yr FN Yorkshire Terrier
- Diagnosed with diabetes mellitus 2 years ago and been on Caninsulin BID
- 2 week history of fussy appetite and over past 48hr inappetant, lethargic, vomiting and diarrhoea.
- No insulin given over the last 48hr

Physical examination

+ Very dull and uninterested in surroundings
+ Tachycardic at 140bpm with poor pulses
+ Pale mucous membranes and tacky
+ Abdominal pain on palpation
+ Vomited post abdominal palpation

Emergency database

+ PCV 48%
+ TS 92g/L
+ Glucose off scale
+ pH 7.18

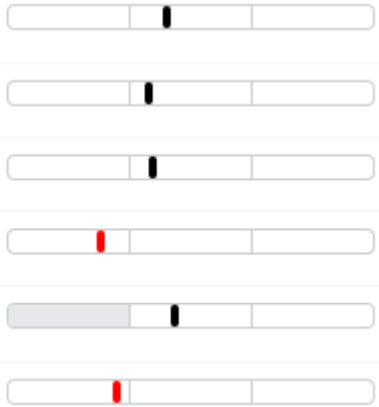
Initial stabilisation

- 0.2mg/kg methadone IV
- 1mg/kg maropitant IV

- 10ml/kg bolus Hartmann's over 10minutes and then reassessed
  - HR 132, poor pulses
- Repeated 10ml/kg/hr bolus
  - HR 120, fair pulses. Systolic blood pressure 85mmHg
- Repeated 5ml/kg/hr bolus
  - Systolic blood pressure 100mmHg HR 100, fair pulses

RBC	6.53	5.83 - 9.01 x10^12/L
Haematocrit	0.429	0.366 - 0.545 L/L
Haemoglobin	161	122 - 184 g/L
MCV	65.7	55.8 - 71.6 fL
MCH	24.6	17.8 - 28.8 pg
MCHC	375	309 - 386 g/L
RDW	14.9	14.7 - 17.9 %
% Reticulocyte	0.6	%
Reticulocytes	41.0	10.0 - 110.0 K/µL
WBC	6.35	5.50 - 16.90 x10^9/L
% Neutrophils	72.9	%
% Lymphocytes	16.4	%
% Monocytes	8.9	%
% Eosinophils	1.2	%
% Basophils	0.6	%

Neutrophils	4.63	2.00 - 12.00 x10^9/L
Lymphocytes	1.04	0.50 - 4.90 x10^9/L
Monocytes	0.56	0.30 - 2.00 x10^9/L
Eosinophils	**0.08**	0.10 - 1.49 x10^9/L
Basophils	0.04	0.00 - 0.10 x10^9/L
Platelets	**165**	175 - 500 x10^9/L



Glucose	43.2	3.6 - 7.0 mmol/L	
IDEXX SDMA	19	1 - 14 µg/dL	
Creatinine	141.0	44.0 - 133.0 µmol/L	
Urea	23.2	3.1 - 10.1 mmol/L	
Sodium	134.8	135.0 - 155.0 mmol/L	
Potassium	4.58	3.60 - 5.60 mmol/L	
Na: K Ratio	29.43	28.80 - 40.00	
Chloride	84.4	100.0 - 116.0 mmol/L	
Total Protein	62.3	54.9 - 75.3 g/L	
Albumin	27.4	26.3 - 38.2 g/L	
Globulin	34.9	23.4 - 42.2 g/L	
Albumin: Globulin Ratio	0.79	0.70 - 1.40	
ALT	17.2	19.8 - 124.0 U/L	
Amylase	1,769.3	100.0 - 1,200.0 U/L	
Lipase	1,863.1	<= 200.0 U/L	

	Urine Appearance	Clear
	Colour	Amber
	Specific Gravity	1.038
	pH	6.0
	Urine Protein	++
	Glucose	++++
	Ketones	+++
	Blood / Haemoglobin	NEGATIVE
	Bilirubin	+
	Urinalysis Test Method	Dipstick/SG measured using Roche U601 analyser.
	White Blood Cells	5-10
	Red Blood Cells	None seen
	Epithelial Cells	None seen
	Casts	Scanty Epithelial cells.
	Crystals	None seen

Address dehydration

- Replacement of hydration losses
  - Deficit (ml) = Body weight (Kg) x % dehydration x 10
    = 8.2 x 10 x 10 = 820ml
- Maintenance requirements
  - Estimated at 60ml/kg/day
  - =492ml
- Ongoing losses
  - Estimated based on volume of vomitus/diarrhoea etc
  - 5 x 10ml = 50ml

  Total = 1362ml/day =57ml/hr

Insulin CRI

+ BG 42mmol/L
+ Added 2.2IU/Kg Neutral insulin to 250ml of 0.9% compound sodium lactate
+ Started insulin CRI at 10ml/hr
+ Hartmann's + KCL given at 47ml/hr

Further blood work

Investigations

+ Haematology
+ Serum biochemistry
+ Urinalysis
+ cPLI
+ Thoracic radiographs
+ Abdominal ultrasound

Abdominal ultrasound

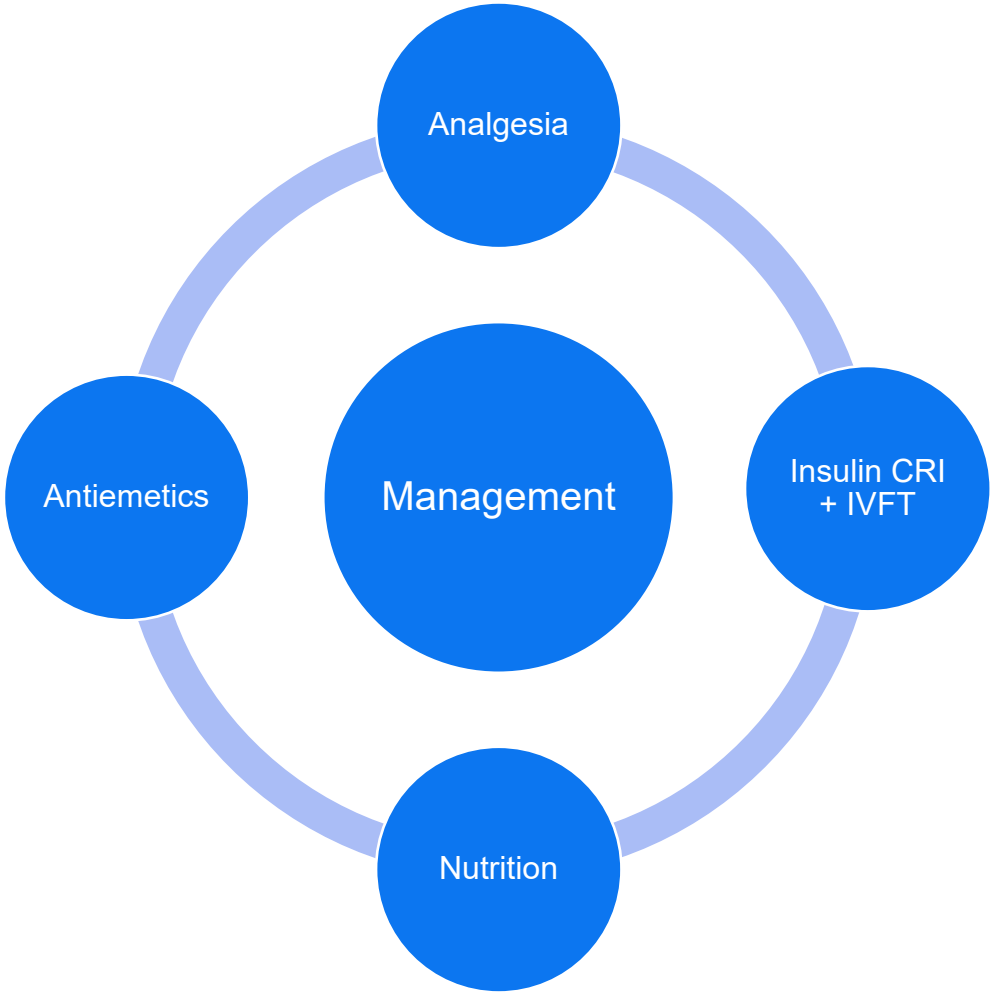
+ Consistent with acute pancreatitis
+ Enlarged, hypoechoic pancreas with surrounding mesenteric fat being hyperechoic. Small volume of effusion in the area of the inflamed pancreas

PANCREATITIS LIKELY INCITING CAUSE OF DKA

Management and outcome

- Started feeding 1/3RER and increased to full RER day 3
- Transitioned to SQ Caninsulin on day 4
- Reduced analgesia gradually and transitioned to paracetamol
- Responded well and eating voluntarily by day 8
- No recurrence of pancreatitis

Management



Summary

+ DKA is life threatening emergency
+ Fluid therapy is critical
+ Insulin regimens vary and best to use what you are most comfortable with
+ Need address concurrent electrolyte abnormalities
+ Investigate and treat underlying concurrent conditions