Application for the support of canine research projects by the Albert-Heim Foundation

Applicant: Katja-Nicole Adamik, PD Dr. med. vet., Diplomate of the American and European College of Veterinary Emergency and Critical Care; Department of Veterinary Clinical Medicine, Division of Small Animal Emergency and Critical Care, Vetsuisse Faculty, University of Bern; Head of emergency and critical care service.

Co-Applicant: Imke Hennink, Dr. med. vet., Cand. Diplomate European College of Veterinary Emergency and Critical Care; Department of Veterinary Clinical Medicine, Division of Small Animal Emergency and Critical Care, Vetsuisse Faculty, University of Bern; Faculty in emergency and critical care service.

1. TITEL

Determination of **H**idden fluid volum**E** and potential fluid ove**R**l**O**ad in canine inten**S**ive care patients. The **HEROS** trial

2. CURRENT STATE OF RESEARCH IN THE PLANNED AREA OF WORK

Intravenous (IV) fluids are the most commonly administered drugs in critically ill patients and the mainstay of management during critical illness. Despite the ubiquitous use, IV fluids are not benign and carry significant risks associated with under- or overadministration, with overdose resulting in possible fluid overload (FO).[1] FO is usually characterized as an expansion of extracellular fluid volume with a positive fluid balance that produces a weight gain of 5-10% from baseline *or* a positive fluid balance of the same magnitude when fluid intake and urine output are measured.[2] Severely ill patients are more susceptible to FO due to an altered salt and water balance, lower water requirements as a consequence of inactivity, and a reduced excretion of fluids with urine.[2-4] The consequences of FO are complications that can affect almost every organ system.[1]

In critically ill people, observational clinical studies have demonstrated an association between FO, adverse events, and mortality.[1] Most of these studies focused exclusively on the resuscitation setting, in which patients need large volumes of fluids over a very short period. In clinical reality though, many fluids and electrolytes are administered for other reasons as well, such as maintenance and replacement therapy over days or weeks. In addition, blood products and enteral liquid nutrition are administered on top of prescribed daily fluid therapy. Moreover, an undocumented but potentially substantial volume of fluids is administered unintentionally as line flushes and diluents or vehicles for IV drugs, what is referred to as hidden fluid volume (HFV).[1,5] In a recent retrospective study in a mixed intensive care unit population (human medicine), HFV represented 32.6% of the mean daily total fluid volume.[6]

In veterinary medicine, data regarding FO are sparse: One retrospective study in critically ill dogs found an increased risk for FO during hospitalization and significant association between FO, illness severity, and mortality.[3] As in human hospitals, fluid therapy is often provided with fluid pumps and critically ill dogs are receiving a standard daily fluid therapy dose of 2-3 ml/kg/h over several days. Furthermore, as in human medicine, it is common practice in veterinary medicine to flush IV lines between and after administration of IV medications and administer some IV medications in a diluted form (e.g., in a dilution of 1:5 over 10 minutes). However, no data exists regarding HFV and its possible impact on FO in critically ill dogs. In particular, small breed dogs (body weight < 6 kg) are likely to be more susceptible to fluid overload than large breed dogs.

With this study, we hope to draw attention to the problem of HFV, improve the management of fluid therapy in canine intensive care patients, and prevent FO and its complications.

3. STATUS OF THE MAIN APPLICANT'S OWN RESEARCH

Katja Adamik is a specialist in small animal emergency and critical care medicine with 20 years of work experience. In addition to her clinical work, Katja designed, supervised and completed, several research projects in the field of fluid therapy and published in peer reviewed journals. A main research area and topic of her habilitation thesis (2018) were synthetic colloids (e.g., hydroxyethyl starch, artificial plasma expander) and hyperosmolar fluids (hypertonic saline and mannitol), and their actions and side effects (e.g., coagulation disorders, renal insufficiency, and tissue retention).

As a second research area, Katja designed, supervised, and published research projects evaluating various biomarkers in dogs with different diseases (SIRS, sepsis, gastric dilatation volvulus, septic peritonitis, orthopedic diseases). The detailed curriculum vitae and publication list can be found in the document sent separately.

4. DETAILED RESEARCH PLAN

Objectives:
First objective–Identification of the volume, the percentage contribution to the prescribed administered volume, and sources of hidden fluids in critically ill dogs.
Second objective–Assessment of hydration and IV-volume status in the study dogs over the length of hospitalization.
Third objective–Evaluation of a correlation between FO and HFV
Forth objective–Analysis whether small dogs are at higher risk for FO due to HFV than large dogs.

Study design: Single center prospective cohort study at the Small Animal Clinic of the Vetsuisse Faculty, University of Bern.

Ethical approval: A signed owner consent will be obtained prior to study inclusion. The study is currently reviewed by the Animal Experiment Committee of the Swiss Federal Veterinary Office (Degree of severity: 0).

Study dogs: We aim to include 100 client-owned dogs in the study. The treatment of each patient is at the discretion of the responsible clinician.
Dogs are grouped into the following 4 weight classes:
Class A: < 10 kg; class B: 11–20 kg; class C: 21–40 kg; class D: > 40 kg.
In order to allow an equal distribution among all groups, 25 dogs per group will be included.

Inclusion criteria:
Dogs presented to the emergency department and subsequently hospitalized for at least 48 hours in the intensive care unit and receiving IV fluid therapy and IV medications.

Exclusion criteria: age <12 months; dogs for which the handling is difficult or dangerous (respiratory distress, uncooperative dogs); history of cardiac disease; cardiac arrhythmia; pleural effusion; gestation/lactation; anemia (hematocrit <20%); end-stage kidney disease with/without renal replacement therapy.

Data collection at admission
Demographic data will include breed, age, gender, and the Acute Patient Physiologic and Laboratory Evaluation ($APPLE_{fast}$)-score (illness severity score).[7] Furthermore, presence/absence of the systemic inflammatory response syndrome with or without infection (sepsis or no sepsis, respectively) will be determined. For the analysis, dogs will then be allocated to different disease groups depending on the patient population.

Standardized monitoring protocol:
In standardized manner (please see attached monitoring sheet) the perfusion status, IV volume status, hydration, and body weight will be assessed at admission and every 24 hours. For this purpose, both clinical parameters and point of care ultrasound (POCUS) are used.[8-10]

The following parameters will be assessed:

Perfusion: mentation, mucous membrane color, capillary refill time, heart rate, rectal temperature, mean arterial pressure (oscillometric or Doppler), and blood lactate concentrations (only if blood sampling is anyway performed).

Hydration: skin turgor, eye position, presence/absence of peripheral edema and/or chemosis, presence/absence of pleural effusion; evaluation for B-lines with POCUS; respiratory rate and effort.

Volume status (POCUS): left atrium-to-aorta ratio (LA/Ao); left ventricular filling; caudal vena cava (CVC) collapsibility index (CVC_{CI}) (subxiphoid view).[8]

Body weight: body weight will be measured always on the same scale in each case and after urination.

Definition of fluid overload:
FO is defined as an increase in body weight >5% (baseline: clinically re-/euhydrated patient) + one of the following: gelatinous skin turgor; peripheral edema and/or chemosis; pleural effusion; development of >3 B lines in at least one view or increase in B lines by >3, respectively; abnormal respiratory effort.
Volume status parameters are evaluated, and trends are documented.

Determination of Hidden Fluid Volume (HFV)
Documentation of fluid administration starts from the time of the first IV catheter (admission) and ends by removal of the last IV catheter. HFV is defined as all IV fluids that are not prescribed on the patient care sheet such as line flushes and diluents or carriers/ diluents for IV medications. The sources of HFV will be identified and quantified as followed:
The administered volume of all IV administered drugs is determined on the basis of the dose for respective patients (patient sheet), as the preparation of powdered drugs or dilutions of injectables is standardized in our hospital. For uncommon medications that are also diluted, the dilution used and thus the total volume administered is documented separately. For fluid flushes (e.g., between medications and for venous catheter control), each patient is provided a daily study flushing kit consisting of:

- Box 1: one plastic box with prefilled saline syringes
  (e.g., 10 x 3 + 10 x 5 ml syringes of saline)
- Box 2: one empty collection box for the used syringes (= residual volume)

Both boxes are taken with the patient (e.g., to anesthesia, surgery) and all flushing is performed only with the syringes from box 1. If sterile syringes for flushing are necessary (e.g., aseptic conditions during central venous catheter placement), completely sterile prefilled syringes will be provided.

The total volume of flushing fluid will be determined every 24 hours by subtracting the volume remaining in the kit from the total volume initially allocated. All prescribed IV fluids (e.g., resuscitation, replacement and maintenance fluids; constant rate infusions of drugs; blood products; parenteral nutrition) and oral liquid nutrition (administered via feeding tube) will be documented daily as well. For every day of hospitalization, the proportion of resuscitation, replacement and maintenance solutions, liquid feeding, blood products (and others) and HFV will be calculated. Further the proportion of HFV *versus* the total volume of prescribed fluids is calculated.

5. FEASIBILITY OF THE STUDY

Patients

Our ICU has 9 places for larger dogs and 2-4 boxes for toy breed dogs (< 6kg) which are usually 80-100% occupied. The authors consider it feasible to include 5 study dogs in parallel/per week (approximate lengths of hospitalization 5 days). Daily examination per dog = 20 minutes once a day (q24h) for 5 dogs = ~100 minutes/day for examination. In addition, counting the syringes and filling the study kits. The investigators will need approximately 20 weeks to include all 100 dogs (+ 3 holiday weeks → July 2023 to December 2024)

Staff

The clinical examinations of the patients and evaluations of the flushing syringes are primarily performed by a specialty intern and future resident in emergency and critical care and one of the applicants. The intensive care unit staff as well as anesthesia and surgery staff will be introduced how to handle the syringes. However, no exact information is provided about the background of the study in order not to bias any results.

6. MILESTONES

	Year 2023							Year 2024					
To do	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**
Information to staff and practice runs													
Inclusion of the study dogs & data sampling													
Statistical analysis													
Writing manuscript													

7. BUDGET

Categories		Cost per sample	Number	Cost
Communication – Staff instruction				
	Printing of posters and handouts (staff instruction)			38.00 €
Patient daily kit				
	Plastic storage boxes with lid (A5 size)	4.50 €	20	90.00 €
	Prefilled Flush Syringes with saline (Streuli AG)	1.25 €	5000	6250.00 €
	Swan-Lock extension set (Covetrus)	3.11 €	200	622.00 €
Divers				
	Printing of monitoring protocols			
TOTAL				**7000.00 €**

8. SIGNIFICANCE OF THE EXPECTED RESULTS AND THEIR IMPLICATIONS FOR THE FUTURE

Although one of the most often prescribed drugs, IV fluids can be harmful and can lead to dangerous FO. In people, the undocumented HFV plays an important role in the development of FO and its negative consequences, such as adverse effects of different organ systems and increased mortality. Data in veterinary medicine are sparse and to the authors' knowledge, there are no data on HFV and very little data on FO in canine intensive care patients. In the context of *'Fluid Stewardship during Critical Illness'* this study explores potential problems and risks of our daily fluid therapy in order to promote a rational and responsible use of IV fluids.

9. SUMMARY AND KEY WORDS

This prospective cohort study evaluates the proportion of different prescribed fluids *versus* the undocumented HFV in a population of 100 critically ill dogs categorized in 4 different weight classes. Further, hydration, perfusion and IV volume status will be evaluated to diagnose a potential FO. Study goals are the identification of the volume, the percentage contribution to the prescribed administered volume, and sources of hidden fluids in critically ill dogs; assessment of hydration and IV-volume status in the study dogs over the length of hospitalization; evaluation of the correlation between FO and HFV; and analysis whether small breed dogs and toy breeds are at higher risk for FO due to HFV than large breed dogs. With this study, we hope to draw attention to the problem of HFV, improve the management of fluid therapy in canine intensive care patients, and prevent FO and its complications.

Key words: Hidden fluids; fluid overload; critically ill; dog; fluid stewardship

Place and date: Bern 1.3.2023

Katja Nicole Adamik

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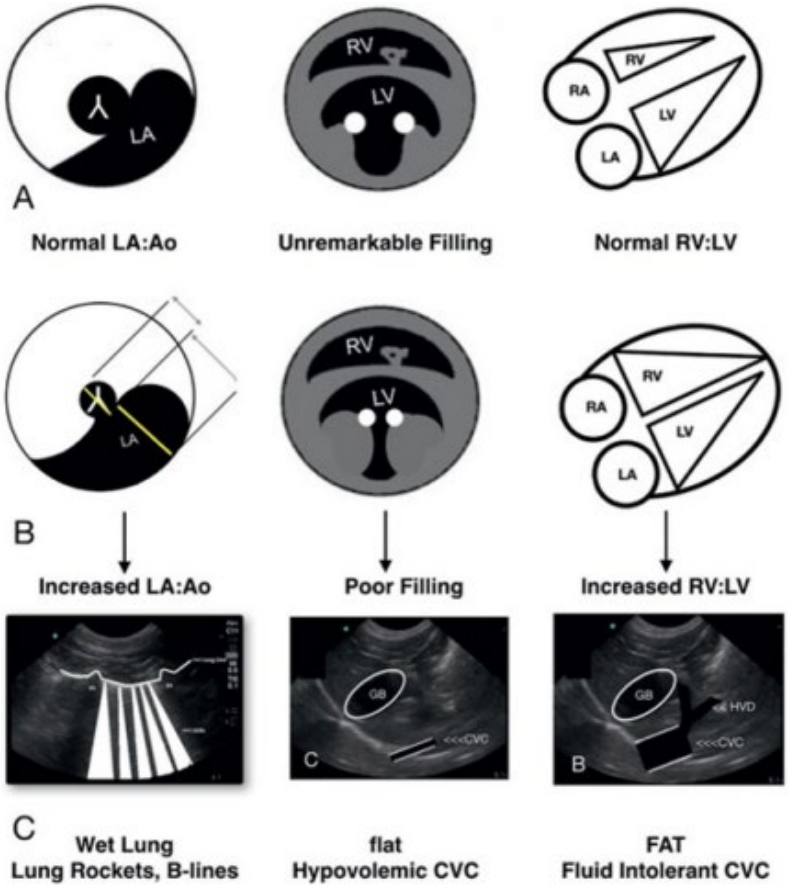
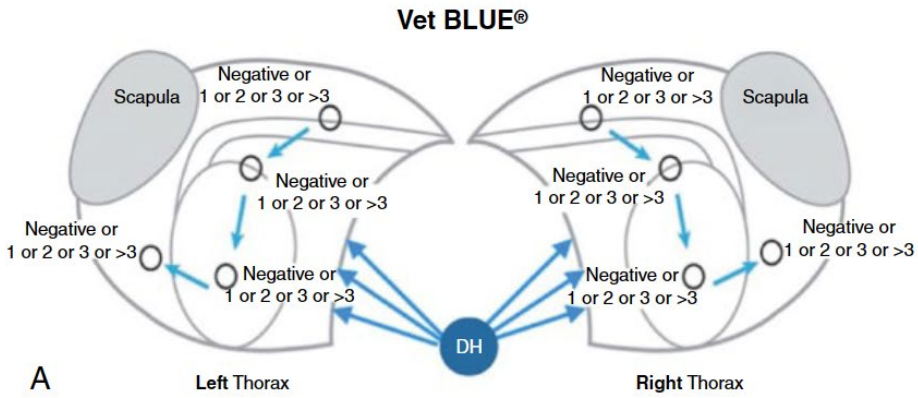
Monitoring protocol HEROS trial

		Admission	Next morning	+24h ⇒ ⇒ ⇒
	Date dd:mm:yy)			
	Time (hh:mm)			
Cardiovascular	SYS/DIA/MAP (oscillo)	1. / / 2. / / 3. / /	1. / / 2. / / 3. / /	1. / / 2. / / 3. / /
	Mentation score (1 to 4)	□ Able to stand unassisted, responsive but dull □ Can stand only when assisted, responsive but dull □ Unable to stand, responsive □ Unable to stand, unresponsive	□ Able to stand unassisted, responsive but dull □ Can stand only when assisted, responsive but dull □ Unable to stand, responsive □ Unable to stand, unresponsive	□ Able to stand unassisted, responsive but dull □ Can stand only when assisted, responsive but dull □ Unable to stand, responsive □ Unable to stand, unresponsive
	MM color	pale/white □ pale-pink □ pink □ red □ other:	pale/white □ pale-pink □ pink □ red □ other:	pale/white □ pale-pink □ pink □ red □ other:
	CRT			
	HR			
	RR			
	Respiratory effort	Normal □ Abnormal □	Normal □ Abnormal □	Normal □ Abnormal □
	Rectal Temp.			
	Extrimity Temp.			
Hydration	Body weight			
	Skin turgor	Reduced □ Normal □ Gelatinous □	Reduced □ Normal □ Gelatinous □	Reduced □ Normal □ Gelatinous □
	Eye position	Sunken □ Normal □	Sunken □ Normal □	Sunken □ Normal □
	Peripheral edema	Yes □ No □	Yes □ No □	Yes □ No □
POCUS & Vet BLUE®	Body cavity fluid score (1 to 3)	□ No free fluid □ Abd. OR thor.OR pericard. free fluid identified □ ≥2 of abd.,thor., and pericard. fluid identified	□ No free fluid □ Abd. OR thor.OR pericard. free fluid identified □ ≥2 of abd.,thor., and pericard. fluid identified	□ No free fluid □ Abd. OR thor.OR pericard. free fluid identified □ ≥2 of abd.,thor., and pericard. fluid identified
	B-lines (Vet BLUE®) (Left Cd, Ph, Md, Cr THEN DH View; Right Cd, Ph, Md, Cr	Left:__, __, __, __ DH:__ Right:__, __, __;__	Left:__, __, __, __ DH:__ Right:__, __, __;__	Left:__, __, __, __ DH:__ Right:__, __, __;__
	LA/Ao ratio	∅LA: ∅Ao:	∅LA: ∅Ao:	∅LA: ∅Ao:
	LV filling (mushroom)	Good filling □ Poor filling □	Good filling □ Poor filling □	Good filling □ Poor filling □
	CVC_{CI} (subxiphoid View)	CVC_{insp}: CVC_{exp}:	CVC_{insp}: CVC_{exp}:	CVC_{insp}: CVC_{exp}:
	Urinary bladder	Longitudinal: L:____ H:____ Transversal W: ____	Longitudinal: L:____ H:____ Transversal W: ____	Longitudinal: L:____ H:____ Transversal W: ____

Global FAST®



Vet BLUE® views (**B**rief **L**unge **U**ltrasound **E**xam)



Quelle: Lisciandro GR, Lisciandro SC. POCUS: Vet BLUE – Clinical Integration In: Lisciandro GR, ed. Point-of-Care Ultrasound Techniques for the Small Animal Practitioner

PERSONAL DATA

Name:	Katja-Nicole Adamik
Degree:	PD Dr. med. vet.
Nationality:	German
Date of birth:	12.12.1974
Languages:	German (first language) English (fluent) French (basic)

EDUCATION

2007 – 2009	Alternate track Residency of ACVECC at the Small Animal Clinic, Department of Veterinary Medicine, Vetsuisse-Faculty University of Bern, Switzerland
6/2002 – 2/2004	Doctoral Student and full time assistant at the Clinic of Small Animals, Faculty of Veterinary Medicine, Free University of Berlin, Germany
10/1998 – 5/2002	Continuation of academic studies of veterinary medicine at the school of Veterinary Medicine, Free University of Berlin, Germany
09/1996 – 09/1998	Academic studies of veterinary medicine at the University of Veterinary Medicine Budapest, Hungary

PROFESSIONAL CAREER

Since 1/2011	Senior lecturer and head of the Emergency and Critical Care Service in the Small Animal Clinic, Department of Veterinary Medicine, Vetsuisse-Faculty University of Bern, Switzerland
01/2007 – 11/2010	Faculty at the Division of Emergency and Critical Care of the Clinic of Small Animal Medicine, Centre for Clinical Veterinary Medicine, Faculty of Veterinary Medicine, LMU Munich, Germany
2007 – 2009	Alternate track Resident of ACVECC at the Small Animal Clinic, Department of Veterinary Medicine, Vetsuisse-Faculty University of Bern, Switzerland
02/2004 – 12/2006	Full time scientific assistant at the Clinic of Small Animals, Faculty of Veterinary Medicine, Free University of Berlin, Germany
2/2002 – 2/2004	Doctoral Student and full time assistant at the Clinic of Small Animals, Faculty of Veterinary Medicine, Free University of Berlin, Germany

CERTIFICATIONS

2018	*Venia docendi* (Privatdozentin) for Emergency and Critical Care

2015	Diplomate ECVECC
2011	Diplomate ACVECC
2006	Doctoral degree (magna cum laude)
2002	Graduation in veterinary medicine

POSTGRADUATE EXTERNSHIPS

4/2009 – 5/2009 (4 weeks)	Clinic of Small Animal Emergency and Critical Care, Department of Surgical and Radiological Sciences, University of California Davis, School of Veterinary Medicine, USA.

FURTHER AREAS OF RESPONSIBILITIES

Head of the small animal clinic blood bank

Director of the small animal internship program at the Vetsuisse University of Bern, and provision of primary mentorship for the interns.

Member of the hygiene commission of the small animal clinic

Program Mentor and administrator of the small animal emergency and critical care residency program (ECVECC)

PUBLICATIONS

2023

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2020

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