In Dogs With a European Adder Bite, Does the Use of Antivenom With Supportive Treatment Compared to Supportive Treatment Alone Improve Time to Recovery?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

Clinical bottom line

The current literature does not offer convincing evidence for the positive effect of antivenom on time to recovery in dogs envenomated by the European adder. It appears that the use of antivenom in addition to supportive treatment may positively affect local swelling if given within 24 hours of the bite, but the evidence is low quality and further studies are required before a more definitive answer can be reached.

Question

In [dogs with European adder bites] does the use of [antivenom and supportive treatment] compared to [supportive treatment only] [improve time to recovery]?

Clinical Scenario

A dog has been brought into your practice with a suspected European adder bite. You do not stock antivenom in the practice and you are aware that it can be difficult to access a source. You wish to know if there is any evidence that giving antivenom will improve the dog's recovery time, compared to supportive treatment alone.

The Evidence

The quality of the evidence available to answer the PICO question is limited by the lack of studies directly comparing the addition of antivenom to supportive treatment alone. At the time of writing no studies were found for the use of antivenom to treat European adder envenomation of dogs with time to recovery used as an outcome. Current studies are limited by bias; the decision to use antivenom is often made on severity of clinical signs, so that only the most severely affected dogs receive it Different sized dogs will also be affected with varying degrees of severity, with some dogs presenting asymptomatically. In addition, different amounts of venom may be injected with some bites injecting no venom (Sutton et al, 2011) so every dog is not subjected to the same amount of venom. These limitations influence the conclusions that can be drawn about the effect of antivenom on time to recovery.

In conclusion, a convincing body of evidence to influence the clinician's decision whether or not to use antivenom in the dog, in addition to supportive treatment, does not currently exist. Other considerations include difficulty in sourcing antivenom (Sutton et al, 2011), so if clinicians decide its use is warranted, they should begin locating a source as soon as possible. Adverse reactions to antivenom have also been reported and a study conducted on 54 dogs found that 7% of the patients developed at least one side effect after administration of F(ab)2 antivenom. The reactions reported in this paper included facial swelling unrelated to the snake bite, profound panting and non-productive cough (Lund et al, 2013); anaphylaxis (Turkovic et al, 2015) has also been reported. At the time of writing, the authors were unable to find any reports of death in dogs directly caused by antivenom administration and Lund et al (2013) state that adverse effects appear to be "relatively mild and self-limiting". As with any drug, the side effects should be considered as part of the decision making process about whether or not to use antivenom.

Summary of the evidence

Lund (2013)	
Population:	● Dogs presented with clinical signs consistent with European adder envenomation and treated with antivenom. ● Dogs were included if either a snake or bite incident was witnessed by the owner or the clinician had identified wounds consistent with fang marks of the European adder.
Sample size:	● Owner questionnaire for 54 dogs envenomated with the European adder and treated with antivenom ● Blood and urine collected and analysed from 35 of the 54 dogs. This was compared to blood and urine collected from a control group of 16 dogs envenomated but not treated with antivenom.
Intervention details:	Administration of 1000 mg F(ab)2 antivenom following envenomation from the European adder.
Study design:	Case series
Outcome studied:	● Questionnaire: ○ Part 1 = signalment (breed, gender, age, weight); bite information (date and time of day of the bite) and whether the owner witnessed the episode; description of dog's reaction and clinical signs; administration of prednisolone by the owner prior to admission. ○ Part 2 = time from bite to admission; dog's mental and physical status; clinical signs at admission; location of the bite; presence of fang marks; type/dosage/effect of treatment. ○ Part 3 = time from bite to administration of antivenom; dose and infusion rate of antivenom; heart rate at 5 minutes intervals following administration of antivenom; resolution of clinical signs and development of adverse effects (type, onset, duration). In case of adverse reactions type, dose and effect of treatment administered was recorded. ○ Part 4 = progression in mental and physical status and clinical signs 24 hours after admission, as well as follow up information at 1 and 2 weeks following admission. ● Blood and urine analysis: ○ Samples were obtained on admission and at 1 and 2 weeks following treatment. ○ Samples were screened for serum globulin, albumin and urine protein levels.
Main findings: (relevant to PICO question):	● Administration of antivenom resulted in a positive effect on mental status and local swelling in all dogs receiving antivenom within 24 hours of the bite occurring. ● 4/54 dogs (7%) developed acute adverse reactions to antivenom:

	o 2 dogs developed facial swelling o 1 dog developed non-productive cough o 1 dog developed sudden, profound panting ● Dogs treated with antivenom had a lower percentage of proteinuria after 2 weeks compared to dogs not treated with antivenom (P = 0.03). ● No differences in serum albumin or globulin were observed between the 2 groups. ● 2/54 dogs treated with antivenom died: ○ 1 due to multiple organ failure after 4 days ○ 1 was euthanased after 5 days due to kidney failure
Limitations:	● Decision to use antivenom was made by different vets on a subjective basis leading to a non-standardised intervention protocol. As a result, the group of dogs receiving antivenom could have been more severely affected compared to the control group of dogs. ● Multiple observers throughout the study and no standardised method for assessment of mental status or local swelling were reported, leading to lack of objectivity in improvements seen with antivenom use. ● Small sample size. ● Study group and control group were not randomly allocated. ● Control group was composed of animals that could not receive antivenom due to cost, lack of availability or deemed unnecessary by the clinician in charge. As a consequence, the control group may include dogs with less severe presentations.

Sutton (2011)	
Population:	● Dogs in the UK reported to the Veterinary Poisons Information Service (VPIS) between September 1985 and December 2010, with European adder bites. ● Questionnaires requesting details of clinical effects, onset and duration of effects, treatments given and clinical outcome are sent to around 55% of enquirers, and patient records were only included if this follow up was complete.
Sample size:	985 enquiries with follow up information from 422 cases and outcomes reported in 411 cases.
Intervention details:	● IVFT used in 241 dogs (57.1 %). ● Antivenom used in 236 dogs (55.9%). ● Supportive treatment included: ○ Glucocorticoids used in 216 dogs. ○ Antibacterial agents used in 235 dogs. ○ Antihistamines used in 84 dogs. ○ Combinations of supportive treatments given to individual dogs were not reported.

Study design:	Case series
Outcome studied:	• Age of dog, weight, sex, breed, month and time of bite and postcode of reporting practice. • Clinical signs reported, onset and duration of clinical signs. • Time to response to antivenom. • Duration of oedema. • Death.
Main findings: (relevant to PICO question):	• Duration of oedema was reported as 46.8 hours in dogs that received antivenom (n=39) and 94.1 hours in those that did not receive antivenom (n=52)(significance unknown - Sutton et al acknowledge that more data is required to calculate significance due to the small number of cases where this outcome was reported). • Response to antivenom reported in 15 dogs; average response time was 74.3 minutes (range 20 minutes to four hours). Method of assessment was not stated. • Death occurred in 7 dogs of 236 receiving antivenom (3%) (unknown if euthanased or died). • Death occurred in 9 dogs of 186 not receiving antivenom (4.8%) (unknown if euthanased or died). • Of the 189 vets that had completed the free comments area of the follow up questionnaire, 33 vets commented that antivenom gave a good clinical response, 18 vets commented that antivenom response time was quick, 11 vets commented that antivenom visibly improved oedema and one vet commented that improvement was faster than without antivenom. Three vets noted that antivenom appeared to have no effect, two vets commented that antivenom made oedema worse and anaphylaxis was reported in one dog following antivenom administration. • Authors of study note that no studies exist on the use of antihistamines for envenomation. As venom causes local histamine release, this may be a future area to study.
Limitations:	• Limited evidentiary value as retrospective review of records. • No controls used. • No information given regarding which dogs received which supportive treatments, so unknown which treatment had effect on clinical signs and time to recovery. • Outcomes were not reported in all dogs, reducing the sample size. • Duration of oedema reported in small number of cases (n=91). • Limited follow up information given and quality of response varied widely. • No statistical analysis of results given, so unknown if outcomes are significant, although author notes that “antivenom administration did not

	appear to affect mortality". ● Not reported how duration of oedema or response to antivenom was assessed. ● Doses of antivenom not reported, so unknown if same dose given to all dogs. ● Information from the free comments area of the questionnaire is opinion. ● Variations in time from envenomation to administration of antivenom may negatively impact effect of antivenom.

Turkovic (2015)	
Population:	Dogs in Germany bitten by the European adder, presented to the Small Animal Clinic at Ludwig-Maximilians University, Munich, between 1st January 2008 and 31st August 2014.
Sample size:	15
Intervention details:	● IVFT used in 15 dogs (crystalloids in all 15 adjusted to hydration status, three also received synthetic colloids). ● Antivenom (Zagreb European Viper Venom Antiserum, 10ml IV) used in eight dogs. ● Supportive treatment included: ○ Fresh frozen plasma (20ml/kg IV) used in five dogs due to coagulopathy. ○ Steroids (prednisolone, 1-2 mg/kg IV) used in ten dogs. ○ Antihistamines (Diphenhydramine, 1-2mg/kg IV) used in 13 dogs. ○ Dopamine CRI (5-10µg/kg/min) used in one dog (due to persistent hypotension & tachycardia). ○ Antibacterial drugs and analgesia used in all dogs. ○ Ranitidine (2mg/kg) used in two dogs.

	○ LMW heparin (100-150 IU SC q 12h) used in eight dogs. Table 2 Treatment in 15 dogs presented after *Vipera berus* bites. Tab. 2 Durchgeführte Behandlung bei 15 Hunden mit Kreuzotterbissen | Pat. no.	Anti-serum	Infusion	Glucocorti-costeroids	Diphen-hydramine	Antibiotics	Analgesics	Dalteparin	Local treatment	Others
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1	–	crystalloid	+	+	amoxi/clav	–	+	–	–
2	–	crystalloid, plasma	+	+	amoxi/clav	–	+	+	–
3	–	crystalloid	+	–	amoxi/clav, enrofloxacin, cefotaxime, clindamycin	buprenorphine	+	+	–
4	+	crystalloid, plasma	+	+	amoxi/clav, enrofloxacin	buprenorphine	+	–	–
5	–	crystalloid, HAES	+	+	amoxi/clav	buprenorphine	–	–	calcium
6	+	crystalloid	–	+	amoxi/clav	fentanyl, butor-phanol	+	–	–
7	+	crystalloid	+	+	amoxi/clav, enrofloxacin, metronidazole	buprenorphine, fentanyl, metamizole	–	–	–
8	+	crystalloid	+	+	amoxi/clav	fentanyl	+	+	ranitidi
9	+	crystalloid	+	+	amoxi/clav	buprenorphine	+	–	ranitidi
10	+	crystalloid, HAES, plasma	+	+	amoxi/clav, enrofloxacin, metronidazole	buprenorphine, fentanyl	+	–	–
11	+	crystalloid	–	+	amoxi/clav, enrofloxacin	buprenorphine, metamizole	–	+	dopami
12	+	crystalloid	–	+	amoxi/clav	fentanyl	–	+	–
13	–	crystalloid, plasma	+	–	amoxi/clav	buprenorphine	–	+	–
14	–	crystalloid	–	+	amoxi/clav	–	–	–	–
15	–	crystalloid, HAES, plasma	–	+	amoxi/clav	metamizole	–	+	–	 Pat. no.: patient number; amoxi/clav: amoxicillin/clavulanic acid; HAES: hydroxyethyl starch; +: yes; –: no Figure1: Breakdown of treatment combinations given to dogs in the study by Turkovic et al, 2015.
Study design:	Case series
Outcomes studied:	• Signalment, date and time of bite, time until presentation, presenting complaint, location of bite, duration of hospitalisation and outcome were studied (if recorded). • Heart rate, respiratory rate, body temperature, mucous membrane colour, capillary refill time, systolic blood pressure, local swelling, packed cell volume (PCV), serum biochemical parameters, electrolytes, platelet count, leukocyte count, blood glucose, activated partial thromboplastin time (aPTT) and prothrombin time (PT) were studied (if recorded).
Main findings: (relevant to PICO question):	• Antivenom administration did not have a significant positive clinical effect on local swelling in the 24 hours following envenomation. • Authors of study note that research into the effects of antihistamines and heparin for treating envenomation in dogs is of interest. • No anaphylaxis was noted following administration of antivenom.
Limitations:	• Individual patient parameters were not reported despite statistical analysis

	being carried out. Data was incomplete and so correlations between treatments and individual changes could not be made or analysed. ● Treatment and outcome monitoring protocols were not standardised making it difficult to compare effects. ● Duration of hospitalisation was recorded for the dogs that did and did not receive antivenom but results were not analysed for significance. ● No controls were used and so it is not possible to demonstrate if antivenom affected outcome. ● Small study size. ● Method of measuring local swelling not stated. ● Retrospective study of patient records so low evidentiary value.

Appraisal, application and reflection

The literature search performed by the authors found three papers which partially addressed the PICO question.

The study by Lund et al (2013) reports an improvement in local swelling and mental status in animals that received antivenom within 24 hours of the European adder bite. The group of dogs receiving antivenom also showed decreased proteinuria levels two weeks after the bite. These findings could be considered of interest when answering the PICO question; the study, however, presents some significant limitations which affect the quality of the evidence produced. The dogs recruited for the study had not been randomly assigned to the antivenom or the control group. The choice to administer antivenom was based on the clinician's subjective assessment of the severity of the clinical signs, the financial situation of the owner and the availability of antivenom. This could have led to the introduction of bias in patient selection. Moreover, the study was not blinded and the subjective improvement noted by the clinicians in swelling and mental status of dogs receiving antivenom cannot be regarded as good quality evidence for the PICO question.

In the Sutton et al (2011) study of cases reported to the VPIS, it was found that in dogs receiving antivenom, oedema lasted an average of 46.8 hours, compared to dogs that did not receive antivenom, where oedema lasted an average of 94.1 hours. This was the most significant finding to the PICO question in this paper but is limited by several factors. Duration of generalised oedema was not reported in all dogs, decreasing the sample size, and objective method of oedema measurement was not given. Statistical analysis of the findings was not reported, so it is not known if the findings are significant. Death occurred in 3% of dogs receiving antivenom and 4.8% of dogs not receiving antivenom, which appears similar, but unfortunately no conclusions can be drawn due to the lack of statistical analysis. The study looked at broad risk factors for envenomation and mortality and the scope of treatment, rather than evaluating the effect of any individual treatment, and this was a common theme among the evidence found.

Turkovic et al (2015) found that antivenom administration did not significantly clinically affect local swelling 24 hours after envenomation, which appears to contrast to the finding from the Lund paper (2013). This paper was another case series studying risk factors, treatments and outcomes, with a very small study size and data relevant to the PICO question was incomplete. Duration of hospitalisation was recorded for dogs receiving and not receiving antivenom but the results were unfortunately not analysed for significance. The use of heparin and antihistamines in treating envenomation were highlighted as future areas of research.

The majority of the studies found by the authors examine risk factors for envenomation, adverse effects of antivenom administration and common treatment choices. Furthermore, most studies were retrospective, considered envenomation by other species or studied the effects of other elements of the treatment regime, such as glucocorticoids. There is wide variation in the combinations of supportive treatment given in the literature; combinations of intravenous fluid therapy (IVFT) with crystalloids, colloids or blood products, analgesia, antibacterial agents, glucocorticoids, antihistamines and heparin (Sutton et al, 2011, Turkovic et al, 2015 and Lund et al, 2013). This lack of a standardised treatment protocol makes direct comparison of the effect of antivenom more difficult to assess. These variations affect the analysis of the impact of antivenom

on time to recovery. The best study design to answer this PICO question would directly compare the outcomes when the use of antivenom is the only variable imposed by the study authors.
The PICO question could be best answered by a prospective, randomised, double-blinded controlled trial, comparing the effects of the addition of antivenom to supportive treatment alone. This could be considered as a research prospect; although a lack of antivenom licensed in dogs and the need to envenomate dogs would render such a study unlikely to pass ethics approval. The relatively small number of dogs envenomated each year in the UK could potentially render such a study financially unviable for antivenom manufacturers. Objective judgement of the clinical effects of antivenom, such as reduction of oedema, also generates difficulties. As such, the proposed clinical trial using ViperaVet may be of interest in revisiting this clinical question in the future; although at the time of writing the study was postponed (VPIS, 2017).

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID Platform 1973 - Week 7 2017 Thomson Reuters Web of Science 1900-2017 PubMed (any date)
Search terms:	1. Dog* OR cani* OR bitch* OR pup* 2. 'Viper* berus' OR 'European adder*' OR 'European viper*' OR adder 3. Antiven* OR antiser* OR anti-ven* OR anti-ser* 4. 1 and 2 5. 1 and 2 and 3 Please note the terms "adder bite*" and "envenomation" were also included in the search strategy, but yielded fewer results than the terms used above and yielded no additional papers.
Dates searches performed:	23/03/2017

Exclusion / Inclusion Criteria	
Exclusion:	● Reviews of available treatments ● Expert opinion ● Letters ● Book chapters ● Papers studying envenomation by species other than the European adder or envenomation of humans ● Papers in a foreign language (that could not reasonably be translated) ● Papers that could not be accessed by authors or library staff
Inclusion:	Studies regarding the use of antivenom for treatment of envenomation of dogs by the European adder, Vipera berus.

Search Outcome								
Database	**Number of results**	**Excluded – Species other than the European adder**	**Excluded – Did not meet PICO question**	**Excluded – Cannot access paper**	**Excluded – Foreign language**	**Excluded - Book chapter**	**Excluded - Duplicate paper**	**Total relevant papers**
CAB Abstracts	18	3	6	0	5	1	0	3
Web of Science	32	2	17	2	0	0	11	0
Pub Med	13	0	2	0	0	0	11	0
Total relevant papers when duplicates removed								**3**

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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