# Hospital contacts after bite by the European adder (Vipera berus)

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## ABSTRACT

**INTRODUCTION:** Bites by the European adder, *Vipera berus,* may cause significant morbidity in bite victims, but this can be reduced through adequate treatment. Since the previous Danish study, a new treatment and a severity grading has been taken into use. The aims of this study were to review clinical cases after a bite from *V. berus* in The North Denmark Region and to evaluate the treatment given.

**METHODS:** In the regional health-care database, we retrospectively identified all patients discharged with the International Classification of Diseases, 10th version (ICD-10) code "T 63.0 snake venom" in the 2007-2013 period. We reviewed patient records for patient demographics, clinical information and information about treatment.

**RESULTS:** During the study period, 76 patients were discharged from a hospital after being bitten by *V. berus* in The North Denmark Region. Envenomation grade 2 or 3 was seen in 61% of victims, and 21% of these were treated with antivenom. T-wave inversion was seen in 9% of the 54 patients in whom an electrocardiography had been performed. The median duration of admittance was 24 hours (mean 48 hours), and risk factors for a prolonged stay at the hospital were grade 2 or 3 envenomation, leukocytosis and moderate/massive oedema at the time of admittance.

**CONCLUSION:** Patients were admitted for a longer time than reported from a previous Danish study on adder bites, and many patients were possibly undertreated with regard to use of antivenom according to recommendations in recent guidelines. No adverse effects were noted due to administration of antivenom. T-wave inversion was observed more frequently than previously described.

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**TRIAL REGISTRATION:** The study was recorded with The North Denmark Region in accordance with a directive from the Danish Data Protection Agency.


The European adder, *Vipera berus,* can be found throughout Denmark except for some of the minor islands. Most *V. berus* bites occur from May to August [1, 2]. The general effect of envenomation may start within the first 10-20 minutes [3]. Victims may experience nausea, abdominal pain, vomiting, incontinence, tachycardia and fainting. Toxin reacts with the vascular endothelial linings, resulting in local oedema and potentially hypovolemia. In severe cases, oedema may spread to the trunk causing hypotension, bleedings, acute renal failure and angioedema [4, 5]. Furthermore, there is some evidence that the venom contains a cardio-toxic component that causes pathological T-wave inversion and myocardial damage [6]. Children, pregnant women and elderly individuals are considered most vulnerable to the venom [7]. Biochemically, neutrophil leukocytosis, elevated serum creatine phosphokinase, elevated creatinine and metabolic acidosis have been described. Haemoglobin may remain high at first, but later anaemia may occur [5].

Adequate treatment may decrease morbidity from bites, and Danish guidelines for treatment have recently been published [8]. The antivenoms ViperaTAb (MicroPharm Ltd, Newcastle Emlyn, United Kingdom) and Viperfav (Sanofi Pasteur SA, Lyon, France) are available for specific treatment of bites. Also corticosteroids have been used for treatment, but the indication for these drugs is controversial [9]. No Danish case series study has so far been undertaken using the recommended envenomation classification [2].

The aims of this study were to describe the clinical presentation, choice of treatment and complications after *V. berus* bites in The North Denmark Region.

## METHODS

### Setting and envenomation severity grading

This descriptive observational case series study was performed in The North Denmark Region where five public hospitals serve approximately 580,000 inhabitants.

The maximum severity of envenomation (grades 0-4) was classified retrospectively by the authors in accordance with the latest Danish guidelines [9]. Grade 0: no envenomation, visible fang marks, but no oedema; grade 1: mild envenomation with local oedema, but no systemic symptoms; grade 2: moderate envenomation with swollen extremity and mild systemic symptoms; grade 3: severe envenomation with oedema on abdomen/trunk, shock, prolonged hypotension, bleedings; grade 4: lethal envenomation, cardiac arrest.

### Data acquisition

We retrospectively identified all patients in the regional health-care database who had been discharged with the International Classification of Diseases, 10th version (ICD-10) code "T 63.0 snake venom" in the period 1 Jan-

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uary 2007 to 1 November 2013. Medical records were accessed electronically by BLH, SKH and SC through Clinical Suite Care (Falls Church, Virginia, USA). Complications and re-admissions were noted up to 90 days after discharge.

### Statistics

We compared categorical variables using the chi-square test. Fisher's exact test was applied when groups comprised less than five patients. Continuous variables were compared using a two-sample t-test (normal distribution) or Wilcoxon rank-sum test (non-normal distribution). Correlation between admission time and severity of envenomation was estimated using the Kruskal-Wallis test. Hypotension was defined as a systolic blood pressure < 90 mmHg. References for biochemistry markers were chosen in accordance with the references used at Aalborg University Hospital. All statistical analyses were carried out using STATA IC 11.0 (StataCorp, College Station, Texas, USA).

### Ethics

Permission from the regional health research ethics committee was not required for a registry-based study.

*Trial registration:* The study was recorded with The North Denmark Region in accordance with a directive from the Danish Data Protection Agency.

## RESULTS

### Description of patients

During the study period, 82 patients were coded "T 63.0". Six patients were considered not to have been bitten by *V. berus*, of whom four had suspected bites by either an insect or a grass snake (*Natrix natrix*); one was bitten by an unknown snake in a terrarium; and one patient was bitten by a *Boa constrictor* in a zoo. Thus, a total of 76 patients were bitten by *V. berus*.

The average number of hospital contacts after a bite from *V. berus* was 11 per year (**Table 1**). The median age of the bite victims was 29 years (interquartile range (IQR): 11-53 years), and the median age was not statistically different for females (34 years) and males (24 years, p = 0.47). The age range was 3-73 years, and 27 (36%) patients were below 14 years of age. Male victims were more likely to be bitten on the upper extremity (58%) than were female victims (23%, p < 0.01). A seven-year-old patient was bitten on the face (lower lip) while crawling on the ground.

### Severity of envenomation

Six (8%) of the patients had grade 0 envenomation, 24 (43%) grade 1, 34 (45%) grade 2 and 12 (16%) grade 3 (**Table 2**). No patients died due to their bite. A higher proportion of patients with grade 3 envenomation were discharged from Aalborg University Hospital (29%) than from the other hospitals (8%, p = 0.02). An elevated creatinine kinase was associated with severity of envenomation (p = 0.02). Arterial blood analysis was performed in 26 patients, three (12%) of whom showed metabolic acidosis and 5 (19%) had respiratory alkalosis compatible with hyperventilation. A total of 24 patients had a urine sample analysed with a dipstick and three patients had detectable erythrocytes. In addition, 54 patients had an electrocardiography (ECG) performed, 5 (9%) of whom showed pathological T-wave inversion. All patients with T-wave inversion had grade 2 or 3 poisoning.

### Controversial first aid measures

In three (4%) cases, the patient or the patient's relatives tried to suck out the venom before arriving at the hospital, and in three other cases a tourniquet was clamped around the affected extremity.

### Treatment and length of hospitalisation

Antivenom was administered to a total of 16 (21%) patients (Table 2) and was more often administered to patients with hypotension (71% versus 29%, p < 0.01) and was only administered to patients with envenomation grade 2 or 3. The type of specific antivenom used was not registered. No adverse effects were noted due to administration of antivenom. There was no difference in the median age of patients receiving antivenom (38 years) and patients not receiving antivenom (29 years, p = 0.65); and the proportion of patients receiving antivenom below 14 years of age (22%) was the same as that of patients aged 14 years or more (20%, p = 0.85). The median length of admission was 24 hours (IQR: 16-48 hours), with a total range of 4–455 hours (mean 48 hours, 95% CI: 33-64 hours). Patients with a moderate/massive oedema on admission were hospitalised for a longer median period of time (59 hours) than patients with a minor oedema (24 hours, p < 0.03), and patients with leukocytosis were hospitalised for a longer median period of time (41 hours) than patients without leukocytosis (22 hours, p < 0.01). The median admission time correlated with severity of envenomation: nine hours (grade 0), 21 hours (grade 1), 36 hours (grade 2) and 59 hours (grade 3) (p < 0.01). For patients with grade 2 envenomation, the median time of admission was not significantly different between those receiving antivenom and those who did not (33 versus 71 hours, p = 0.24), but the number of patients fulfilling these criteria was too small to detect a difference.

### Complications and sequelae

Five (7%) patients were transferred to an intensive care unit (ICU), four of whom were treated with antivenom. The median time of hospitalisation for patients requiring intensive care was 48 hours. The patient bitten on the

lower lip was observed in the ICU for two hours, but no severe reaction occurred, and the patient was discharged from the hospital after 16 hours. One patient developed deep vein thrombosis during hospitalisation, and another patient was diagnosed with pulmonary embolus. The latter subsequently had a coronary artery bypass graft inserted and was hospitalised for a total of 19 days (455 hours). One patient was diagnosed with pneumonia during admission, but no patients developed compartment syndrome. Three (4%) patients developed anaemia during admission, and one patient had to be readmitted due to anaemia which was discovered eight days after discharge. Two patients were readmitted within 90 days after discharge due to prolonged oedema.

## DISCUSSION

In this observational case series study, we describe the clinical course of 76 patients bitten by *V. berus* in The North Denmark Region during a seven-year period. The median duration of admittance was 24 hours (mean 48 hours), and risk factors for a prolonged stay at the hospital were grade 2 or 3 envenomation and leukocytosis.

The civil registration system in Denmark provided the opportunity to systematically identify all patients discharged from a hospital in The North Denmark Region with the ICD-10 code "T 63.0 snake venom". A previous systematic study of bite victims in Denmark presented data from 31 patients seeking care at Ringkøbing Hospital from 1995 to 2000 [2]. The study found a mean time of admission of 20 hours. Another investigation from Regional Hospital Herning evaluating 10 cases found a mean admission duration of 28 hours [10]; thus, both were lower than in our study. In the study from Ringkøbing Hospital, the authors reported that 35% had moderate envenomation and none had severe envenomation compared with 45% and 16% of the patients with grades 2 and 3 in our study, respectively. Although the two grading systems are slightly different, it is clear that patients with more severe envenomation were observed in our study, which may be why 37% our patients were admitted at the referral hospital (Aalborg University Hospital) where a larger proportion of patients had grade 3 envenomation. Symptoms following bite from *V. berus* are well described in the literature [2, 3-7]. We found a high proportion of patients with T-wave inversion on ECG, although not all patients had the analysis performed. In a Swedish nationwide study including 231 patients, 4% of the symptomatic patients had ECG changes [6]. Another Swedish study found T-wave inversion among 2 (7%) of 30 patients [11]. Cardiac infarction and arrest after a bite have occurred on rare occasions [6, 12, 13], which emphasises the need for cardiac monitoring [2]. The exact cause why patients had been bitten was not registered in the medical records, but relatively more males than females were bitten on the upper extremity, which suggests that males were more likely to attempt picking up snakes.

Several severe complications may occur after a bite. One patient developed a pulmonary embolus, a complication that has been described elsewhere [14]. Patients

**TABLE 1**

Presentation of 76 patients bitten by *Vipera berus*.

| | Population | % |
|---|---|---|
| *Gender* | | |
| Male | 41 | 54 |
| Female | 35 | 46 |
| *Age, yrs* | | |
| < 11 | 18 | 24 |
| 11–20 | 14 | 18 |
| 21–30 | 8 | 11 |
| 31–40 | 6 | 7 |
| 41–50 | 9 | 12 |
| 51–60 | 13 | 17 |
| 61–70 | 4 | 5 |
| > 70 | 4 | 5 |
| *Nationality* | | |
| Danish | 57 | 75 |
| German | 15 | 20 |
| Other[a] | 4 | 5 |
| *Tourist* | | |
| Yes | 39 | 51 |
| No | 37 | 49 |
| *Location of bite* | | |
| Lower extremity | 44 | 58 |
| Upper extremity | 31 | 41 |
| Face | 1 | 1 |
| *Fang marks* | | |
| Single | 10 | 13 |
| Double | 20 | 26 |
| > 2 marks | 15 | 20 |
| Unknown | 31 | 41 |
| *Hospital* | | |
| Aalborg University Hospital | 28 | 37 |
| Vendsyssel Hospital | 27 | 36 |
| Thy-Mors Hospital | 17 | 22 |
| Hobro Hospital | 3 | 4 |
| Dronninglund Hospital | 1 | 1 |
| *Hospitalisation* | | |
| Yes | 73 | 96 |
| No | 3 | 4 |
| *Year of bite* | | |
| 2007 | 9 | 12 |
| 2008 | 12 | 16 |
| 2009 | 10 | 13 |
| 2010 | 9 | 12 |
| 2011 | 14 | 18 |
| 2012 | 10 | 13 |
| 2013 | 12 | 16 |

a) Other nationalities: 1 Swedish, 1 Norwegian, 1 Swiss and 1 Filipino.

TABLE 2

Clinical data, laboratory data and treatment of patients after arrival at the hospital. The values are n (%).

| | Grade of envenoming | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | Total |
| Patients, n | 6 | 24 | 34 | 12 | 7 6 |
| *Symptoms* | | | | | |
| Nausea | 0 (0) | 1 (4) | 17 (50) | 8 (75) | 27 (36) |
| Vomiting | 0 (0) | 1 (4) | 10 (29) | 8 (67) | 19 (25) |
| Stomach pain | 0 (0) | 0 (0) | 9 (26) | 9 (75) | 18 (23) |
| Shock | 0 (0) | 0 (0) | 4 (12) | 3 (25) | 7 (9) |
| Dyspnoea | 0 (0) | 0 (0) | 2 (6) | 3 (25) | 5 (7) |
| Unconsciousness | 0 (0) | 0 (0) | 1 (3) | 3 (25) | 4 (5) |
| Diarrhoea | 0 (0) | 0 (0) | 1 (3) | 2 (17) | 3 (4) |
| *Oedema*[a] | | | | | |
| None | 5 (83) | 2 (8) | 2 (6) | 0 (0) | 9 (12) |
| Local | 1 (17) | 19 (79) | 12 (35) | 9 (75) | 41 (54) |
| Mild | 0 (0) | 2 (8) | 14 (41) | 1 (8) | 17 (23) |
| Moderate | 0 (0) | 0 (0) | 6 (18) | 1 (8) | 7 (9) |
| Massive | 0 (0) | 0 (0) | 0 (0) | 1 (8) | 1 (1) |
| Unknown | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 1 (1) |
| *Systolic blood pressure* | | | | | |
| Normal | 5 (83) | 19 (79) | 32 (94) | 6 (50) | 62 (82) |
| Hypotension: < 90 mmHg | 0 (0) | 1 (4) | 0 (0) | 6 (50) | 7 (9) |
| Unknown | 1 (17) | 4 (17) | 2 (6) | 0 (0) | 7 (9) |
| *Heart rate* | | | | | |
| Normocardia | 3 (50) | 15 (63) | 22 (64) | 6 (50) | 46 (61) |
| Tachycardia: pulse > 100 | 0 (0) | 2 (8) | 8 (24) | 2 (17) | 12 (16) |
| Unknown | 3 (50) | 7 (29) | 4 (12) | 4 (33) | 18 (24) |
| *Haemoglobin level* | | | | | |
| Normal | 3 (50) | 16 (67) | 21 (62) | 9 (75) | 49 (64) |
| Anaemia: | | | | | |
| haemoglobin conc. < 8.3 mmol/l | 0 (0) | 1 (4) | 2 (6) | 1 (8) | 4 (5) |
| Unknown | 3 (50) | 7 (29) | 11 (32) | 2 (17) | 23 (30) |
| *Leukocyte cell count* | | | | | |
| Normal | 3 (50) | 10 (42) | 6 (18) | 1 (8) | 20 (26) |
| Elevated: > 10.0 × $10^9$ cells/l | 0 (0) | 7 (29) | 17 (50) | 9 (75) | 33 (43) |
| Unknown | 3 (50) | 7 (29) | 11 (32) | 2 (17) | 23 (30) |
| *C-reactive protein level* | | | | | |
| Normal | 1 (17) | 7 (29) | 10 (29) | 3 (25) | 21 (28) |
| Elevated: > 8.0 mg/l | 2 (33) | 9 (38) | 13 (38) | 6 (50) | 30 (39) |
| Unknown | 3 (50) | 8 (33) | 11 (32) | 3 (25) | 25 (33) |
| *INR* | | | | | |
| Normal | 1 (17) | 5 (21) | 4 (12) | 2 (17) | 12 (16) |
| Elevated: > 1.0 | 2 (33) | 10 (42) | 16 (47) | 8 (67) | 36 (47) |
| Unknown | 3 (50) | 9 (37) | 14 (41) | 2 (17) | 28 (37) |
| *D-dimer level* | | | | | |
| Normal | 1 (17) | 4 (17) | 3 (9) | 1 (8) | 9 (12) |
| Elevated: > 0.3 mg/l | 1 (17) | 4 (17) | 9 (26) | 7 (58) | 21 (28) |
| Unknown | 4 (67) | 16 (67) | 22 (65) | 4 (33) | 46 (61) |
| *Creatinine kinase level* | | | | | |
| Normal | 0 (0) | 9 (38) | 9 (27) | 6 (50) | 24 (32) |
| Elevated:> 150 U/l | 3 (50) | 1 (4) | 10 (29) | 2 (17) | 16 (21) |
| Unknown | 3 (50) | 14 (58) | 15 (44) | 4 (33) | 35 (47) |
| *Myoglobin level* | | | | | |
| Normal | 1 (17) | 5 (21) | 4 (12) | 5 (42) | 15 (20) |
| Elevated: > 74 µg/l | 0 (0) | 1 (4) | 4 (12) | 1 (8) | 6 (8) |
| Unknown | 5 (83) | 18 (75) | 26 (76) | 6 (50) | 55 (72) |

TABLE 2, CONTINUED

| | Grade of envenoming | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | Total |
| *Treatment* | | | | | |
| Antivenom | 0 (0) | 0 (0) | 6 (18) | 10 (83) | 16 (21) |
| Tetanus prophylaxis | 0 (0) | 9 (39) | 11 (32) | 6 (50) | 26 (35) |
| Paracetamol | 0 (0) | 13 (54) | 23 (68) | 10 (83) | 46 (61) |
| Other pain killers | 0 (0) | 6 (25) | 16 (47) | 5 (42) | 27 (36) |
| IV fluids | 0 (0) | 2 (8) | 14 (41) | 12 (100) | 28 (37) |
| Adrenalin | 0 (0) | 0 (0) | 2 (3) | 8 (67) | 9 (12) |
| Thrombosis prophylaxis | 0 (0) | 0 (0) | 3 (9) | 5 (42) | 8 (11) |
| Antiemetics | 0 (0) | 0 (0) | 4 (12) | 3 (25) | 7 (9) |
| Antibiotics | 0 (0) | 0 (0) | 4 (12) | 1 (8) | 5 (7) |
| Antihistamin | 0 (0) | 7 (29) | 18 (53) | 9 (75) | 34 (45) |
| Corticosteroids | 0 (0) | 6 (25) | 12 (35) | 10 (83) | 28 (37) |

INR = international normalised ratio; IV = intraveneous.
a) local = hand/foot, mild = to the knee/elbow, moderate = the whole extremity, massive = involving abdomen/truncus.

are at risk of developing compartment syndrome [15, 16]; however, this occurred in none of our patients. A bite in the facial region may potentially threaten the airways [17], causing our patient, who was bitten in the lower lip, to be observed at the ICU.

In three patients, an attempt was made to suck out the venom, which is not recommended due to the risk of introducing venom into a wound of the person doing the procedure. Clamping a tourniquet around the extremity may cause hypoperfusion and necrosis [4, 18, 19]. Corticosteroids were widely used for treatment, but a recent French study did not find that corticosteroids improved outcome [10]. The same study reported that infusion of antivenom within ten hours after the bite significantly reduced the incidence of haematomas, functional discomfort and length of hospital stay. According to the recommendations by Weile et al, administration of antivenom should be considered for patients with grade 2 or 3 envenomation and for patient in whom envenomation grade increases. According to our grading, 16/46 (35%) patients with grade 2 or 3 envenomation received antivenom, which indicated undertreatment in a large proportion of patients. In contrast, the Swedish study reported that 42 (18%) of 229 patients received antivenom, including 27/55 (49%) patients with moderate or severe envenomation [6]. Unfortunately, the medical records did not contain information on the type of antivenom product used. In this study, the maximum grade of envenomation during hospitalisation was noted retrospectively by the investigators as this information was not available in the medical records. We recommend that the grade of envenomation should be registered in medical records at the time of hospitalisation and that patients should be observed for progression and eventually be reclassified according to the maximal severity grade.

Due to the retrospective design ensuing from the use of an ICD-10 code to identify patients, selection bias may have been introduced. In our study, 8% of patients were without symptoms of envenomation compared with the 30% often described in the literature [4, 5]. This may be because patients without symptoms were less likely to seek medical attention at the hospital or because asymptomatic patients had a shorter length of hospitalisation which possibly reduced the likelihood of having the correct ICD-10 code registered at discharge [20]. Data were incomplete in some of the patients' medical records, in particular data on laboratory analyses. Thus, patients with more severe envenomation were more likely to have blood tests performed. This also introduced selection bias, and data should therefore be interpreted with caution.

## CONCLUSION

In this region-wide study, we presented 76 patients bitten by *V. berus*. The patients were admitted for a longer time than reported in a previous Danish study, and many patients were possibly undertreated according to the recommendations in recent guidelines with regard to use of antivenom. No adverse effects were noted due to administration of antivenom. Although not recommended, many patients received corticosteroids, and training of emergency personnel is warranted as local guidelines are updated. T-wave inversion was observed more frequently than previously described.

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