Antitoxin use and pediatric intensive care for viper bites in Rome, Italy

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Abstract. – In Italy viper bites represent an uncommon event, though envenomation can cause severe complications, more in children than adults, because of dose/body size ratio. We present a case series within a selected population: 10 Italian cases (from Rome surroundings) of viperbites requiring PICU admission, over a 5-year interval. Five children showed a systemic involvement, whereas the remaining patients showed a damage. All were managed and closely monitored in an ICU setting. Relevant clinical findings and therapeutic approach, ICU course and complications have been recorded. Age range was 3-15 years with mean age of 6,9 (SD±4,58) years; 2 patients needed respiratory support beyond oxygen supplementation. Most patients underwent fluid loading, while hemodynamic support was given to 4/10. Median PICU stay was 60 hours (IQR=24.0-75.5). No mortality was reported. Indications and precautions for administration of antivenom in the last years have been reviewed: early treatment seems to reduce mortality/morbidity, though representing a threat for children. Current recommendations for the treatment of viper envenomation have been described, based on a literature's review and the application of these knowledges to clinical reality of our PICUs. Therefore, paediatric patients with systemic or rapidly evolving symptoms should be monitored carefully for the development of bite-related complications in an ICU setting mostly in younger children.

Key Words:
　Viper bites, Children envenomation, Antivenin treatment.

Introduction

Four species of poisonous snakes are present in Italy: the common viper (Vipera Aspis), spread throughout the country; the Vipera Berus, distributed in the Alps; the Vipera Ammotydes who lives in the mountainous and hilly regions of North-East Italy; the Vipera Ursini, spread only over 1400 mt in the mountains of Abruzzo, Umbria and Marche, whose bite is never fatal. Rome surroundings are known as a very-low incidence area for viper bites and children undergoing viper envenomation are rarely admitted to Pediatric Intensive Care Unit (PICU).

The available epidemiological data are unreliable because fragmentary, though it has been approximated that the annual incidence approaches 3/100.000 in different regions of Europe[1]. In Italy the incidence can reach 5/100.000, morbidity is around 1/100.000 and mortality rate is 0.1-0.2%[2,3]; the Health National Institute data attests only one fatality caused by the bite of venomous snakes from 2003 to 2006.

There are no uniform national guidelines for management (including indications for Intensive Care Unit (ICU) admission and treatment) for children snake-bitten by Vipera Aspis, the most abundant venomous snake in the country. The grading proposed by Audebert in 1992, nowadays universally adopted, allows a clear distinction between moderate and severe envenomation: both conditions can represent clinical settings requiring antivenom treatment[4].

Patients and Methods

All patients admitted to both PICUs ("Bambino Gesù" Children Hospital and "Gemelli" Hospital) following a snake bite from May 2005 to January 2010 have been included. Patients with minor clinical effects were left out of scope of this survey. 10 patients were enrolled and 5 of these presented a clear systemic involvement. For clinical evaluation we used a modified "Snakebite Severity Score" (SSS)[5], whereas for the administration

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of antiofidic serum the Audebert grading scale was preferred[6] (Table I).

Illustrative Cases: Systemic Involvement

Case 1

A 3-year-old female, body weight (BW) 14 kg, was bitten by a viper while she was playing in a garden near a rural area. The dead snake was then brought for identification (Figure 1F). On first evaluation, she was unable to report the bite and an ecchymotic lesion (left foot) was misdiagnosed as accidental or traumatic. After a few hours, haemorrhagic oedema and swelling were well above her knee, and the child developed diarrhoea and vomiting. On arrival at PICU, she was pale, sweaty and confused. There was a marked haemorrhagic swelling of the entire left leg: the skin was ecchymotic and tender (Figure 1C-E). Heart rate (HR) was 220 bpm and arterial pressure was 65/45, no urine output was reported recently. Peripheral venous cannulation was impossible and a central line was placed after midazolam/ketamine analgo-sedation. The right femoral artery was then cannulated for blood pressure (BP) monitoring. During the first 12 hours, the child needed up to 2 lt of colloid-crystalloid solutions to overcome the shock status (fluid bolus of 280 ml and daily manteinance for the first 12 hours of 10 ml/kg/h). Intravenous hydrocortisone (50 mg) and cefotaxime (700 mg) were also administered. A nasogastric tube was inserted due to vomiting. Within 8 hours from admission, the oedema reached the abdominal wall and the lower chest (Figure 1A-B). Despite the leg enlargement and tenderness, both the pedidia and the posterior tibial arteries were palpable and Doppler tracing showed the maintenance of arterial flow. Routine biochemical studies on admission reported marked hyperglycemia (345 mg/dL), creatinine 1,5 mg/dL, Na 129 mEq/L, K 5.1 mEq/L, LDH and CPK were 516 U/L and 1382 U/L respectively. Coagulation studies showed a raised D-dimer level > 1000 g/L, INR increased to 1.8 and leukocytosis (14.8×10^9/L). Antivenom was infused intravenously. When the oedema reached the chest wall spontaneous ventilation was impaired. She was given IV fenoldopam to improve renal flow as well as insulin infusion and IV pentoxifylline and Iloprost. A capillary leak syndrome developed and she needed mask-CPAP, that solved the hypoxemic respiratory distress in 10 hours; there was no

Table I. Grade of envenoming subsequent to viper bites (V. Aspis and V.berus)[6].

Audebert severity score		
0	No envenomation	No oedema, no fang marks
1	Minimal envenomation	Local oedema around the bite area - No systemic symptoms
2	Moderate envenomation	Regional oedema involving a major part of limb - Moderate systemic symptoms (slight hypotension, vomiting, diarrhea)
3	Severe envenomation	Extensive oedema spreading into the trunk, severe systemic symptoms (prolonged hypotension, shock, bleeding)

need to switch to other ventilatory supports. Her clinical condition stabilized within 24 hours. The haemorrhagic residual oedema of the left leg solved over 2 weeks.

Case 5

A 20 month-old male, BW of 10 kg, bitten by a snake in a garden, experienced an immediate onset of respiratory symptoms (tachypnea and dyspnoea). He was given IV methylprednisolone (20 mg/kg) and nebulised adrenaline by the emergency transport team and then transferred to PICU. On admission, he presented with oedema and ecchymosis of the first toe and the metatarsal of his right foot. A generalized skin rash, fever (39.5°C), widespread bronchospasm, BP 90/55 mmHg and HR of 190 bpm were also noticed. After the administration of equine anti-snake venom, he showed a sudden cardiorespiratory deterioration, requiring intubation and mechanical ventilation. On this regard the worsening of the clinical condition could be a side effect of the antivenom or the progression of venom toxicity. Blood tests showed leukocytosis (23.3×10^9/L), and coagulation profiles still within limits. Saline fluid load (40 ml/kg) and iv dopamine (5-8 mcg/kg/min for 40 hours), 30 mg/kg methylprednisolone and perphenazine were administered, achieving hemodynamic improvement. Antibiotic therapy (ceftriaxone and amikacin) were also given. After 36 hours, blood tests showed increased creatine phosphokinase (CPK 783 UI/L) and lactate dehydrogenase (LDH 1700 UI/L), which have returned to normal within 48 hours. Oedema of the foot was limited to the malleolar region and, therefore, it was deemed not necessary further antivenom administration. The patient was estubated 36

Figure 1. Clinical picture of a severe viper bite envenomation, presenting with severe hypovolemic shock. A capillary leak syndrome was evidenced early during the clinical course, together with an increased oxygen need due to pulmonary oedema *(A, B)*. The haemorrhagic/oedematous area progressed rapidly towards the trunk *(C-E)*, involving the abdominal wall and – to some extent – the chest. The viper was then found and retrieved by the parents *(F)*. (Publication permission obtained).

hours after admission and his progressive clinical improvement allowed the discharge 5 days later.

Case 6

A 15-year-old patient, BW 50 kg, was bitten on the second finger of his left hand. After PICU admission, the oedema rapidly reached the ipsilateral shoulder, with increasing pain and signs of lymphangitis. Blood tests showed a deterioration of the coagulation profile, having normal values of CPK, myoglobin and myoglobinuria. During viper antiserum administration recurrent skin rashes involving the trunk occurred, together with marked bronchospasm, requiring 10 mg/kg IV hydrocortisone and chlorphenamine and adrenaline nebulization. Intensive care monitoring was necessary, together with ceftriaxone (2 g) and tramadol continuous infusion (max dose 600 mg/die). The Doppler US showed no signs of blood flow obstruction on the affected upper limb.

The clinical picture improved after serum administration, paralleling a progressive reduction of limb oedema. There was no need of ventilatory support, nor signs of respiratory distress. PICU discharge was performed on the fourth day.

Case 7

A 3-year-old patient, BW 15 kg, was hospitalized in the intensive area, after being bitten by a viper at the right thumb. He presented with progressive hard oedema interesting the whole limb and the omolateral axilla. Besides cardio-respiratory parameters within limits (tachycardia responded to fluids 6ml/kg and paracetamol as analgesic agent), he showed hyperglycemia (over 180 mg/dl) and leukocytosis (WBC 17.2×10^9/L with neutrophils 15.5×10^9/L). US Doppler assessment of the limb circulation was negative for flow obstruction. Due to the progression of swelling-oedema, 5 hours after bite, a dose of equine serum

anti-viper venom was administered intravenously, achieving the arrest of progression and local condition improvement. No further systemic signs appeared, thus allowing PICU discharge at 48 hours from admission.

Case 10

An 8-year-old male was found unresponsive while playing in a rural area. A viper bite was identified on a finger of the right hand. The rescue team noticed a worsening respiratory distress with tongue oedema and bilateral chest rales; both subcutaneous epinephrine and IV fluids (500 ml) were given for initial resuscitation. High-dose IV steroids (hydrocortisone 100 mg) were also administered. Right hand became increasingly oedematous, including the wrist: both radial and ulnar arterial pulses were present, while a wide ecchymosis appeared within the swollen skin area. On PICU admission, the patient was alert, though still hypotensive and tachycardic. His oxygen saturation was 90% on FiO_2 0.30. After full hemodynamic monitoring was accomplished, a further fluid loading was performed, and an inotropic agent (5-7 mcg/kg/min dopamine) was added. Cardiorespiratory status progressively improved over the next 8-12 hours; however, the local condition underwent a rapid progression towards the entire arm (Figure 2 A-C) and Antivenin (European Viper Venom antiserum) administration was performed at 12 hours post-admission.

Biology of Venomous Effect

In humans (and animals), viper snake bite has 2 major effects: synergistic effect of several proteolytic enzymes (phospholipase A_2, hialuronidase, proteases, metalloproteinases) on the vessel wall that cause locally an intense inflammation associated with pain that increases as a result of centripetal oedema that may also affect chest and abdomen, often causing further blood loss and/or vascular thrombosis. Few hours after venom injection lymphangitis and appearance of diffuse bruising may occur. Local oedema can be intense, with the possible occurrence of compartment syndrome, sometimes requiring aponeurotomy. Local complications such as tissue necrosis are more common in children.

Systemic signs may also appear before local because hemodynamic findings may be either immediate, unrelated to the amount of venom inoculated (anaphylaxis reactions) or can increasingly develop, depending on the venom toxicity, because the

Figure 2. A-C. Clinical findings of upper arm viper bite, demonstrating the progression of the lesion towards the shoulder. In this patient, the upper limit of the haemorrhagic oedema is evident (publication permission obtained). As outlined, the progression of the oedematous/haemorrhagic area towards the trunk may be very rapid.

increasing concentrations of venom protein in the blood, causing generalised symptoms such as hypotension and abdominal cramps, vomiting and diarrhoea, allergic sensitisation (asthma, laryngeal or facial edema), consumption coagulopathy potentially leading to DIC (the most feared condition[7]) and, rarely, death. A capillary-leak syndrome was demonstrated in young patients whose abdomen and thorax were extensively affected. Among systemic complications, widespread rhabdomyolysis is of particular interest[8]. Muscle damage could be of multifactorial origin: capillary leak syndrome plays a main role because the limb oedema induced by enhanced capillary permeability can result in tissue hypoperfusion followed by ischemia, with further muscle cell lesions. In some cases renal failure, shock[9,10], central nervous system disorders (dysphonia[11], bilateral ptosis[12], external ophtalmoplegia, parasthesias, dysphagia)[13-16] can also be present. Blood count may demonstrate normochromic anaemia, sometimes severe (can be manifest one or more days after the bite and may be explained by haematoma, bleeding in the swollen limb, and the need for massive fluid replacement), neutrophilic leukocytosis, and thrombocytopenia. Elongation of both partial thromboplastin time (aPTT) and prothrombin time (PT), hypofibrinogenemia, increased fibrinogen degradation factors (FDP) may witness coagulation derangement.

The potential pathogen effects may also be related to the interaction of the poison with the host tissue, so local and general clinical manifestations are influenced by several factors, as the amount of injected snake venom and the seriousness of the poisoning[17]. Of paramount importance, the demonstration of possible antagonization of TNF-related hemodynamic depression in an experimental setting of viper-bite envenomation[18].

Discussion

Among the four species of potentially poisonous snakes in Italy, only three are actually involved in accidental viper bites; venom composition is very similar without clinical differences: envenomation occurs in 20-30% of reported bites and in most instances causes only minor local symptoms. Even if rare, systemic complications may be fatal. Overall mortality is very low, less than 1% in some series, but it is possibly higher in children because the amount of poison injected is greater in relation to the size of the body[20]. Male gender, living in rural areas, summer months and

daytime were found to be risk factors for Viper Bites[17]. Pain, oedema and ecchymosis are most common findings and sometimes younger children are unable to report the event, with the risk of delayed diagnosis[21]. On the other side, many PICU admissions are induced by the fear of systemic toxicity due to the viper envenomation or to the need for antivenin therapy and related risks[3]. Vipera venom has hematotoxic effects on platelet counts, coagulation parameters (PT, aPTT, fibrinogen, FDP), serum electrolytes, LDH, urinalysis, urinary output and vital markers should be monitored regularly in all cases. In fact, hematologic lab derangements are always reported in viper bite victims, possibly as a response against toxins or acute stress. Among previous studies, Ozay et al[17] reported 21% thrombocytopenia (< 120,000/mm^3) and 54% leukocytosis. Our laboratory evaluation revealed leukocytosis (range14.8-23.3x10^9/L), PT/aPTT prolongation and raised D-dimer level (> 1000 g/l) as a result of endothelial activation. Significant risk factors for the development of a severe complication, such as DIC, tissue necrosis or compartment syndrome, were high grading score, increased AST (> 50 IU/L), thrombocytopenia and large ecchymosis area[17]. Although mortality can be lowered by intensive care and management, DIC remains the most common cause of death.

We herein report the experience of viper bite victims admitted to PICU over a 5-year period in Rome, Italy. This area is traditionally thought as a very-low-incidence region for viper bites envenomation compared to Italian mountain regions and other European countries. Data from systematic analysis of viper bite envenomation in Italian children are scarce: severe envenomation appear to account only for 8% of total reported cases in an Italian survey of 1988[2]. Although snake bites can occur at all ages, prepubertal period is the most common for childhood and the mean bite age has been reported to be 6.5 years, more prone to snake bites because they usually play outside and they are more active.The prevalence is lower in preschool ages (age 0-5), while children less than 3 years old are generally protected from snake bites because they usually stay at home, do not go out alone, and when outdoors they are usually with caretakers. When snakebite occurs, the patient is carried to the nearest healthcare unit without delay.

In our study the age range was 3-15 years with the mean age of6, 9 (SD±4.58) years. Most of the snake-bitten children are male and this is demonstrated also in this series (9:1). Bites are mostly

seen on feet and hands: in our series 7/10 children were bitten on the hands. To classify our snake bites patients we used the clinical grading score of Audebert and the SSS. Naturally Audebert score was 2 or 3, a criteria for PICU admission, while SSS was ranged between 2-14 (mean SSS 8.10±4.01) (Table II).

The progression of haemorrhagic/oedematous area was most frequently restricted to the entire extremity where the child was bitten (till the shoulder for the bitten hands like in Figure 2A-C, until the malleolus or knee for the feet as evident in Figure 1C-E). Only one case reported a progression towards the abdomen and thorax, and the SSS in this patient, the only girl present in this series, was 14. Systemic complications have been recorded in 50% of patients: most important complications were hypovolemic shock and capillary leak syndrome as in Figure 1A-B (1 case), anaphylactic shock (1), rhabdomyolisis (3 cases) with myoglobinuria.

Coagulative impairment (marked derangement in 5cases), leukocytosis (7 cases) and hyperglycaemia (5) were all present in our series. Respiratory failure or airway oedema (2), gastrointestinal signs with vomiting and diarrhoea (1), stupor (1), extra ocular muscle paresis (1) were less common. At PICU admission all patients received IV steroids, antibiotic prophylaxis and analgesia; 5/10 enoxaparin (useful to prevent thrombotic events), 4/10 dopamine and/or epinephrine, 2/10 Fenoldopam (to improve renal flow). Overall, 7/10 patients required fluid load, while most patients received oxygen supplementation.

The issue of antivenin treatment of patients after snakebite has been controversial for decades[20]. The benign natural history of the great majority of bites by European vipers has accounted in the past for many treatments, sometimes bizarre, whether in the field or in hospital. In mild cases, simple observation is adequate, while moderate forms are hospitalized for at least 24 hours for possible clinical worsening. Grade 2 paediatric patients should be admitted to ICU and immediately treated with intravenous fluids (sometimes abundant) and with antivenom[22,23]. According to Audebert et al[4], antivenom therapy should be offered also to grade 2 patients, on the basis of significant blood/urine venom concentrations. "Serum antivenins" administration raised serious concerns in the past, because they were associated with severe complications (reported deaths from anaphylaxis) especially in cases of repeated administration[24]. In hospital all grade 0 patients should be observed at least for

three hours, in order to reveal possible clinical evolution. Younger children need special observation, for a minimum of 24 hours, because they may not show the characteristic signs, often having an unexpected evolution. Grade 3 children should be quickly admitted to ICU.

In our series, Antivenom administration was performed following PICU admission on the basis of both immediate severity and early clinical worsening. It was performed in 8 patients while 6 patients had delayed administration (2-24hours) according to clinical progression. In these patients coagulopathy reflected systemic toxicity of viper venom, that is a definite borderline indication for antivenom administration. However, clinical improvement was achieved in all reported cases, with a median PICU length of stay of 60 hours (IQR 24.0-75.5). Subsequently, children were discharged to a paediatric ward to continue clinical observation.

Therapeutic approach is based on cleaning and disinfection of the wound, compression bandage and immobilization of the affected limb, associated with antibiotics and analgesics[21]. Truthfully compression bandage is recommended just in some case, in which systemic toxicity is life threatening. Tetanus toxoid was injected to all cases irrespective of the bite site. Corticosteroids and adrenaline are useful mostly in case of allergic reactions, although subcutaneous adrenaline seems to be effective also in reducing adverse reactions of antivenin serum[25]. The indications for antivenom administration (equine Fab or ovine Fab[26]) would be the following: circulatory instability poorly responsive to symptomatic treatment or relapsing, rapid progression of oedematous/ecchymotic area, protracted or recurring gastrointestinal symptoms, mucous membrane swelling, fluctuating level of consciousness, peripheral or cranial nerve paresis[25]. In borderline cases, one or more of the following conditions may strengthen the indication: leukocytosis (> 15-20x10^9/L), metabolic acidosis, haemolysis, coagulation disorders and electrocardiographic changes. The administration of anti-snake venom serum must be performed within a hospital setting, to control possible hypersensitivity reactions. An equal dose is administered to children as to adults. The serum is infused slowly via IV injection (5 to 10 minutes) or better in solution with normal saline over 30 minutes. Some authors recommend a skin test with 0.1 ml diluted antivenom intradermally, to check for allergy, but this is controversial.

Table II. clinical characteristics of viper bite children admitted to PICU during the study period. Table Legend: LF left foot; RF right foot; LH left hand; RH, right hand, S, survived; SSS snakebite severity score (adapted from Peterson ME[19]).

Pt n.	age/gender	Bite site	Clin grading Audebert	SSS	Progression (max level)	Antivenin (Y/N) (delay)	Complications	Medical treatment	Outcome (PICU length of stay -hrs)
1	3F	LF	3	14	Abdomen, thorax	Yes (24h)	Hypovolemic shock, capillary leak, coagulative impairment, severe rhabdomyolysis- myoglobinuria, leukocytosis, hyperglycemia	Fluid load, dopamine, enoxaparin, steroids, fenoldopam	S (245)
2	4M	LH	3	6	Arm, shoulder	Yes	Coagulative impairment (INR > 1.5)	Fluid load, Enoxaparin, steroids,	S (48)
3	14M	RH	2	10	Entire arm	Yes	Hyperglycemia, mild rhabdomyolysis (CPK 1341), leukocytosis	Fluid load, Enoxaparin, steroids,	S (24)
4	8M	RH	2	4	Elbow	No	Vomiting, diarrhea	Steroids	S (24)
5	3M	RF	3	10	Foot, malleolus	Yes (2h)	Respiratory failure, Skin rash,	MV 24 hrs, fluid load, dopamine, steroids	S (72)
6	8M	RH	3	12	Entire arm	Yes (8 h)	Tongue oedema, stupor; rhabdomyolysis (CPK 2270), leukocytosis	Fluid load, Steroids, dopamine, NSAIDs	S (72)
7	15M	LH	3	5	Shoulder, clavicle	Yes (18h)	Coagulative impairment, leukocytosis, hyperglycemia	Fluid load, Steroids,	S (72)
8	3M	RH	2	6	Shoulder	Yes (24h)	Hyperglycemia	Steroids, enoxaparin	S (48)
9	3 M	LF	2	2	Foot, malleolus	No	Leukocytosis, coagulative impairment	Steroids	S (24)
10	8M	RH	3	12	Shoulder	Yes (12h)	Anaphylactic shock, coagulative impairment, drowsiness, airway oedema, leukocytosis, hyperglycemia	Fluid load, Epinephrine, steroids, dopamine, fenoldopam, enoxaparin-oxygen suppl, NSAIDS	S (86)

Conclusions

Even in low-incidence regions, viper bite envenomation in infants/children represent a life-threatening event requiring immediate management. Such a uncommon event can be misdiagnosed and delayed recognition may delay appropriate management. Victims should be monitored closely and carefully for the development of bite-related complications. Intensive care units can provide the adequate level of monitoring and care for snakebite envenomation, mostly in younger children.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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