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Snake envenomings in French Guiana: first clinical assessment of a new antivenom.

Envenimations ophidiennes en Guyane française : première évaluation clinique d'un nouveau sérum antivenimeux.

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BIBLIOGRAPHIC REFERENCES

ANNEXES

Snake envenomings in French Guiana: first clinical assessment of a new antivenom.

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Abstract:

Introduction

Ophidian envenomation in French Guiana is a potentially severe matter, as it can be life-threatening and can cause functional after-effects on the bitten limb. Immunotherapy is the specific reference treatment but it was not available on the territory. In November 2014, a collaboration between the Saint Laurent du Maroni Hospital and the Western France Poison Control Center (PCC) set up a protocol in order to efficiently treat envenomation cases. A stock of Antivipmyn-Tri® antivenom was made available. The purpose of this study is to assess the tolerability and efficacy of immunotherapy using the Antivipmyn-Tri®, as well as gather epidemiological data on envenomed patients in Saint Laurent du Maroni in order to improve treatment of ophidian envenomation in the whole region.

Methods

This prospective and observational study includes all *Crotalinae* related ophidian envenomation cases - between November 2014 and June 2016 - admitted to the Saint Laurent du Maroni Hospital and that required advice from the Western France PCC.

Results

Thirty envenomation cases were counted. Envenomation mainly concerned male subjects (77%), between 15 and 65 years old (73%, averaging 36 years old), mostly in rainy season, during work or a walk in the forest at the end of the day. The circumstances are mainly accidental and snakebites are located in the lower limb. The final severity was divided into 0 grade 0, 1 grade I, 24 grades II and 5 grades III. The hospitalization lasted on average of 6 days. 26 patients who received Antivipmyn-Tri® showed stabilisation and a regression of their clinical signs along with a significant improvement, often standardization, of their PT and fibrinogen. No cases of severe anaphylactic reactions and no deaths were reported during this study.

Conclusion

Antivipmyn-Tri® is currently the only effective antivenom able to treat venomous bites from French Guiana snakes. It is both effective and well-tolerated. In the future, it is of vital importance to offer standardised treatment methods across the whole French Guiana region. To this end, it is necessary to keep assessing the current immunotherapy that uses Antivipmyn-Tri®, for tolerance and effectiveness.

INTRODUCTION

The Situation in French Guiana

1) The Envenomation Problem:

French Guiana is a low populated French department and most of its people are gathered in urban areas. The Amazonian forest (1) that covers its territory is populated with dangerous snakes (2).

In 2009, the World Health Organisation (WHO) declared ophidian envenomation a "neglected tropical disease" (3,4). In fact, venomous snake bites are a public health issue neglected in many tropical and subtropical countries, world-wide (5,6).

2) Epidemiology of ophidian envenomation:

Human activity conditions man and snake encounters and potential envenomation. Even if some snakes, like *Bothrops atrox,* venture into urban areas (7). The population that is most affected by ophidian envenomation is comprised of working men (7,8). Snakebites usually occur during the night, at dusk or at dawn, during farm work or moving through forests (9).

There is no recent epidemiological data regarding the number of annual envenomation cases in French Guiana, although it would allow for easier treatment. Data are disseminated: Incidence is estimated by means of isolated epidemiological surveys, morbidity through health facility records, and mortality through the civil register (10). The annual incidence of snakebites in 2002 was less than 50/100,000 inhabitants in urban areas, and it reached 600/100,000 inhabitants in primary forests (7). This is a reason to seek emergency services and call the regulation centre at the Emergency Medical Service: in 1998 and 2001, ophidian aggression was the second reason among fauna aggression calls (11).

3) Ophidian Fauna in French Guiana:

An abundant ophidian fauna populates the primary forests that cover 95% of the Guiana territory, a French department in South America (7). Eighty-five species are identified and, among them, eleven are venomous (12). The main types of snakes responsible for envenomation belong to the *Crotalinae* sub-species in the *Viperidae* family, as well as – although less often – to the *Elapidae* family (coral snakes) (7).

The most identified *Crotalinae* are (9,13):
- *Bothrops atrox*, "common lancehead", the most frequent aggressor (7) ,which often ventures into inhabited areas.
- *Bothrops brazili*, "Brazil's lancehead" or "small-scaled lancehead", mainly in the forest.
- *Crotalus durissus*, "tropical rattlesnake" in the coastal savannah.
- *Lachesis muta*, "mute rattlesnake" or "large-scaled lancehead", also in the forest.
- *Bothrops bilineatus*, arboreal and nocturnal.

Envenomations by snakes of the *Elapidae* family, *Micrurus*-type coral snakes – especially *Micrurus surinamensis* and *Micrurus lemniscatus* – show few local signs but do cause an important neurotoxic syndrome (14). These types of evonomation are extremely rare and that is why there is no existing published data on the subject in French Guiana.

Consequences of Ophidian Envenomation

Ophidian envenomation is potentially serious, threatening life in the short term, as well as posing a medium and long-term risk of experiencing functional after-effects in the bitten limb (3,4,15,16). The number of cases is moderate compared to the ophidian population in the territory (7). Envenomation seriousness depends on venom toxicity and, therefore, on the snake species and the dose of venom injected (17,18). The composition of venoms varies from one family to another (8,19). The venom composition of the *Viperidae* family is rich in protein and enzymes (20,21,22), which are mostly proteolytic. A venomous bite produces a viper syndrome, i.e., an inflammatory syndrome (intense pain and oedema), extended and local necrosis or coagulation disorders (23,24) such as coagulopathy associated to the activation and consumption of platelets and coagulation factors (25). The main consequence is a haemorrhagic syndrome that may be life threatening (haemorrhagic shock, intracerebral haemorrhage). On some occasions, as with *Crotalus durissus*, we can also identify a cobra syndrome with neuromuscular disorders (which may cause paralysis of the respiratory muscles and death by asphyxia), as well as delayed nephrotoxicity (14). In addition, bite wounds may get infected (anaerobic germs) and lead to sepsis if they are not treated adequately (26).

Use of Antivenom (AV) in French Guiana

Before immunotherapy, envenomation treatment was symptomatic (8,12,27). However, symptomatic treatment is complex and, generally, not enough.

Today, antivenom immunotherapy is the reference treatment for ophidian envenomation globally (23). Like all medicinal products, it can cause side effects like serum sickness (28) but with current product purity it's rare (29,30). It is safe, effective by reducing morbidity, mortality and treatment costs for envenomation patients. It improves the benefit-risk balance (31,32,33). Indicated in grade-II and grade-III envenomation, it neutralizes and accelerates venom elimination (34). It must be adapted to the identified species. If the species has not been identified, it may be adapted to the clinic and be polyvalent. When immunotherapy is indicated, treatment must be started as soon as possible, with enough doses and through the intravenous route of administration (3,20).

At the moment, the main limitations for its use are: availability of appropriate good-quality serum, proven to be efficient and well tolerated as well as the fear or ignorance regarding antivenom immunotherapy. Moreover, there is a shortage of such cheap serum (10,35,36,37,38).

An antivenom was used for the first time in French Guiana during the 1980's. It produced tolerance problems so it was not used again. Since then, and despite the

number of envenomation, there had not been any specific treatment available in the French Guiana territory. Therefore, progress was sometimes unfavourable, there were functional after-effects in the bitten limb, and it was often necessary to resort to surgery. After a long period of rejection (related to the side effects of antivenoms), the production of antivenoms has significantly improved (8) alongside better manufacturing practices (39,40,41), guaranteeing a safe use. Antivenoms are made of entire immunoglobulin G or fragmented F(ab)2 or Fab molecules (42,43) that constitute a hyperimmune serum (44).

As a response, in November 2014, due to an initiative by the Saint Laurent du Maroni Hospital and the Western France Poison Control Centre (PCC), based on the knowledge and experience provided by the Antivenom Bank (14,45,46), a stock of Antivipmyn-Tri® antivenom becomes available, and a treatment protocol for envenomation patients is put into practice. Antivipmyn-Tri® is an antivenom efficient for the *Viperidae* species mentioned above, such as *Bothrops atrox*, *Bothrops brazili*, *Crotalus durissus*, *Lachesis muta*, and *Bothrops bilineatus* (8).

Study Objectives:

The purpose of this study is to evaluate the tolerability and efficacy of immunotherapy with Antivipmyn-Tri®, as well as to submit epidemiological data of patients envenomed in French Guiana at Saint Laurent du Maroni hospital to improve the treatment of ophidian envenomation in the territory.

METHODS

Study Type:

Observational prospective study including all cases of ophidian envenomation by *Crotalinae* occurring between November 2014 and June 2016 treated at the Saint Laurent du Maroni Hospital in French Guiana that lead to advice being sought from the Western France PCC.

The two teams that collaborated on this study are the Western France PCC and the Saint Laurent du Maroni hospital. Although the latter is not the biggest hospital in the region, it is strategically located on the doorstep of the Amazonian forest and is therefore very much concerned with the issue of ophidian envenomations. That is why it was willing to import and use the antivenom.

Antivenom:

The only immunotherapy used was Antivipmyn-Tri® imported from Mexico. It is an immune serum F(ab')2 with high neutralizing power (200 to 780 DL50 mouse/ampoule depending on the species), active in certain species of the *Bothrops*, *Crotalus*, *Lachesis*, *Sistrurus* and *Agkistrodon* families (14). Among the antivenom which are available and effective for French Guiana snakes, this one is chosen for the Temporary Use Authorization issued by the French Agency for the Safety of Medicines and Health Products, and it has already been used within the Antivenom Bank.

Protocol:

The protocol mentioned in the Annex was elaborated and validated by different experts and by the teams of the Saint Laurent du Maroni Hospital and the Western France PCC.

Immunotherapy with Antivipmyn-Tri® is recommended from grade II onwards in the protocol.

The proposed dosage is a dose of three 10-mL ampoules in 125 mL of NaCI 9% for adults and 60 mL for children in an hour. It was decided to administer three ampoules first. This dose is renewable if necessary, depending on clinical and biological factors.

Immunotherapy was performed at the Saint Laurent du Maroni Hospital, and the pharmacy prescribed the medications with the patient's consent.

Graduation of Severity:

This antivenom was administered according to the clinical and biological grades indicated in ***Table I***. These grades are: grade 0 (white snap without envenomation), grade I (minimal envenomation), grade II (moderate envenomation) and grade III (severe envenomation).

Collected data were classified in a table grouping the epidemiological and clinical-biological criteria evaluated in the treatment protocol. Patients were enumerated in the chronological order of their bites.

Table I: Graduation of Severity of Guyanese Snake Envenomation Except Micrurus:

<table>
<tr><td rowspan="2">Grade</td><td colspan="3">CLINICAL SIGNS (at least one criterion defines the grade)</td><td rowspan="2">BIOLOGICAL SIGNS (at least one criterion defines the grade)</td></tr>
<tr><td>Viper syndrome</td><td>General signs</td><td>Neurotoxic syndrome</td></tr>
<tr><td>0</td><td>- Moderate Pain, fang marks.
- No oedema.
- No haemorrhage.</td><td>None</td><td>None</td><td>None</td></tr>
<tr><td>1</td><td>- Intense pain.
-The oedema does not surpass the underlying joint
- No haemorrhage.</td><td>None</td><td>None</td><td>=> minor hemostasis disorders:
- 80Giga/L<Platelets < 150Giga/L
- 45%<PT<70%
- 1g/L<fibrinogen<2g/L</td></tr>
<tr><td>2</td><td>- The oedema surpasses the underlying joint
- Blister(s), mild necrosis.
- Moderate bleeding at the site of the bite, haematuria, and gum bleeding.</td><td>- Digestive signs (diarrhoea, vomiting, abdominal pain).
- Hemodynamic Signs (tachycardia, hypotension).
- Thoracic pain.</td><td>Ptosis, diplopia, mydriasis, deglutition problems, myasthenic syndrome, fasciculation, myalgia, flaccid paralysis.</td><td>=> Coagulopathy :
- Platelets<80Giga/L
- PT<45%-TCAx2
- Fibrinogen <1g/L
=> Impaired renal function : Creatinine > 120µmol/L
=> Rhabdomyolysis : CPK 1000UI/l</td></tr>
<tr><td rowspan="2">3</td><td rowspan="2">- Oedema reaching or surpassing the limb root, extended necrosis.
- Severe haemorrhage (epistaxis, haemoptysis, gastrointestinal bleeding)</td><td>State of shock.</td><td>Respiratory difficulty.</td><td rowspan="2">Coagulopathy
et
Haemoglobin<9g/dL</td></tr>
<tr><td colspan="2">Coma, Seizure.</td></tr>
<tr><td colspan="4">• Higher grade if: - pregnant
- <11 or >60 years old
- body weight <25kg
- bite in face or neck</td></tr>
</table>

Data Collection:

Data are collected from Western France PCC envenomation case sheets registered during the corresponding period. The data obtained were completed with hospitalisation mail, biological reports made during hospitalisation and, in more recent cases, with full protocols transmitted by the Saint Laurent du Maroni Hospital. Data related to calls to the Western France PCC were extracted from the PCC database authorised by the French National Data Processing Committee (Accreditation n°747735).

Population, Inclusion Criteria, and Clinical and Biological Parameters Studied:

We recorded all cases of patients bitten by a snake of the family of *Viperidae*, under family of *Crotalinae*, type *Crotalus, Bothrops* and *Lachesis* (presence of typical fang marks and recognition of the snake, patient's history).

The following parameters were evaluated: age, gender, patient profile, the severity of envenomation, snake species, circumstances of the snake bite, the time between the snake bite and hospitalisation and between the snake bite and Antivipmyn-Tri® administration, the doses of Antivipmyn-Tri®, sign of intolerance, duration of hospitalisation, resort to the surgery, symptoms and coagulation status before and after immunotherapy.

The symptoms of the snake bite were collected. The envenomation severity was based on protocol graduation (established by the protocol in force at Saint Laurent du Maroni Hospital and the Western France PCC protocol for viper envenomation in France (47), based to Audebert's clinical severity grading (48)).

Each patient received clinical (systemic signs, neurological signs, swelling, haematoma, necrosis) and biological follow up. The biological severity criteria were: thrombocytes < 80 G/l, PT (prothrombin time) < 45%, fibrinogen < 1 g/L and creatinine > 120 µmol/L.

The reference values are the ones used in the laboratory at Saint Laurent du Maroni, where the extractions were made.

In coagulation report analyses, before immunotherapy, the reference value was the lowest one identified at admission, and after immunotherapy, it was the value identified before discharge.

RESULTS

Epidemiology

1) Bite

Between November 2014 and June 2016, thirty cases of envenomation were collected.

Distribution per season indicates a snakebite peak during the rainy season (***Table II***) according to F. Starace's calendar (9): twenty-three cases during the rainy season against seven cases during the dry season. These occurred at midday, with twenty-two cases between midday and midnight, with a peak between 5 and 8 pm (twelve cases).

Table II: Seasonal distribution of snakebites (evaluated from December 2014 to June 2016, i.e. about two rain season and one dry season)

	Number of month	Number of snake bite	Average number of snake bites per month
Dry season	6	7	1,2
Rain season	13	23	1,8

Among the thirty cases, the site of the bite and the circumstances were identified in twenty-seven patients. Snakebite circumstances are mainly accidental. Snakebites occurred mainly in the forest (seventeen cases). Among them, at gold mining sites, two occurred in children (playing situations) and four occurred whilst moving. Eight cases were identified on the periphery of green areas and gardens: six times, in children playing, and twice in adults. A snakebite case occurred during farm labour, and another one in an urban context. No bite during animal manipulation was reported.

Among the thirty cases, the snake was seen twenty-one times. It was identified by the victim fifteen times: fourteen as a "lancehead" and once as a *Bothrops Brazili.* Two snakes were detected with a formal identification: A *Bothrops Brazili* and a *Lachesis Muta.* As regards snakebite cases during that period, we identified a case of envenomation by *Micrurus* with favourable progress, which was not included in the study.

Snakebites are mostly located in the lower limbs, below the knees (twenty-eight cases). Two cases of snakebite in the upper limbs were identified, one during farm work and another one during gold mining activities.

2) Population

Table III shows a description of the general characteristics of the population.

This study showed that envenomation mainly concerned male subjects. Most of them are between 15 and 65 years old, a mean of 37.5 years old, averaging 36 years old. A

third of the cases occurred in children (< 18 years old) who were playing or walking through the forest, and a third of the cases occurred in clandestine workers. The grade of all bites treated at Saint Laurent du Maroni was greater than or equal to I. The final severity was: zero grade 0 (or white bite), one grade I, twenty-four grade II, and five grade III.

Table III: Description of population: 30 patients included.

Variable	Mode	Population n= 30	Percentage %
Gender	Male	23	76,67
	Female	7	23,33
Age (years)	<15	7	23,33
	15-65	22	73,34
	>65	1	3,33
Localisation morsure	Superior member	2	6,67
	Inferior member	28	93,33
Grade	0	0	0
	I	1	3,33
	II	24	80
	III	5	16,67
ANTIVIPMYN TRI	Single dose	22	73,34
	Multiple doses	4	13,33
	0	4	13,33
Duration of hospital stay (day)	<7d	24	80
	7-10d	4	13,33
	>10d	2	6,67

3) Hospital Stay Duration

Hospital stays lasted 1 to 34 days. Most patients (twenty-four cases, 80%) stayed in hospital for less than 7 days. On average, hospitalisation of envenomed patients lasted 6 days, with a mean of 4 days. In at least three cases of patients hospitalised for less than 3 days, treatment was performed at the Short-Term Hospitalisation Unit only, and there was no hospitalisation at a clinical service.

The time between the bite and the Antivenom injection, if ordered and administered, was recorded in twenty-three patients, and it varies from 3 to 42 hours, with a 15-hour average (***Table IV***). For this sample (twenty-three patients), average hospitalisation duration was 7 days (greater than the average for the whole series). The patients who received an antivenom injection within 15 hours had an average hospitalisation of 5.7-days. For those who received the injection after 15 hours, average hospitalisation was 9.5-days long.

The period between the bite and hospitalisation was recorded in twenty-seven cases and varies from 1 hour to 41 hours, with an average of 9.6 hours and a 4-hour mean.

Table IV: Time Between Snakebite and Injection of AV (23 Patients):

Duration between snake bite and injection of Antivenom (Hours)	N° Patient	Grade Envenomation	Duration of Hospitalization (Days)
3	14	II	8
3	30	II	2
3,5	19	II	4
4	25	II	28
5,5	5	II	4
6	15	II	4
6	18	II	2
6	28	II	10
9	10	II	6
9	16	II	2
10	29	II	6
11,5	27	II	3
12	2	II	6
12	21	III	5
12,5	8	II	1
13	26	II	1
19	23	III	4
20	1	III	34
22	9	III	4
38	11	II	9
38,5	3	II	5
39	12	II	3
42	20	III	3

Clinical before Immunotherapy

Table V shows the clinical symptoms.

Viper syndrome with pain is preeminent (approximately 80% of grade-II patients) and locoregional signs with oedema in all grade-II and -III patients (except one grade II unknown), with a distinction in development depending on the grade.

Patient with systemic signs are: Patient 1, with grade-III envenomation. He came in a state of shock with hypotension (systolic blood pressure: 75 mmHg) and tachycardia, with 135 beats per minute. Elevated blood pressure was identified in patient 7 et 19, whose history is unknown.

Patient 7 also had mild gastrointestinal signs, with nausea. Patient 8 had a vomiting episode.

No thoracic pain or neurotoxic signs were described in this series of patients.

Two patients showed abscesses at the site of the bite (patients 9 and 25).

As regards renal function, three patients with acute renal failure were identified. Patient 1, grade III, without a history. The identified snake is a “lancehead”. The patient's creatinine is 143 µmol/L before immunotherapy and 150 µmol/L after immunotherapy. Patient 20, grade III, without a history. The snake was not identified.

The patient's creatinine is 240 µmol/L before immunotherapy without other recorded values. Finally, patient 7, grade II. This patient's initial creatinine was normal, 101 µmol/L, but it increased to 187 µmol/L after immunotherapy. This patient's history is unknown, and the snake was identified as a "lancehead".

Table V: Clinical Signs According to the Grade of Envenomation.

	Envenomation Graduation			
	Grade II		Grade III	
CLINICAL SIGNS	Population n=24	Percentage %	Population n=5	Percentage %
Pain	19	79,17	100	100
Edema not exceeding the overlying joint	3	12,5	0	0
Edema beyond the overlying joint	20	83,3	2	40
Edema greater than or equal to the root of the limb	0	0	3	60
Moderate hemorrhage	5	20,83	3	60
Severe hemorrhage	0	0	0	0
Hemodynamic signs	0	0	1	20
Digestive signs	2	8,33	0	0
Chest pain	0	0	0	0
Neurotoxic signs	0	0	0	0
Impaired renal function	1	4,17	2	40

Coagulopathy before Immunotherapy

All patients treated with immunotherapy (grades II and III: twenty-nine patients) had coagulation disorder or collapsed balance sheet of coagulation at admission. Signs of moderate haemorrhage are described (gum bleeding, haemorrhagic blister, moderate haemorrhage at the site of the bite or hematoma) in five grade-II patients (20%) and three grade-III patients (60%).

Among the twenty-seven patients whose PT was recorded at admission, fourteen had a PT greater than or equal to 10%. Nine had a PT between 11 and 45%. Two had a PT between 45 and 70%. None of them had a normal PT, higher than 70% (***Table VI***).

Table VI: Initial PT and Haemorrhagic Signs:

	Grade II																					Grade III			
N° Patient	2	3	5	6	7	8	10	13	14	15	16	17	18	19	22	24	25	26	27	28	29	30	1	9	20	23
PT (N 70-100%) before immunotherapy	<10	21	<10	57	<10	10	18	<10	44	<10	<10	20	55	<10	<10	<10	20	<10	18	17	27	<10	<10	22	45	<10
Clinical haemorrhagic signs	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	No	Yes	No	Yes	No

Among twenty-four patients whose fibrinogens were recorded at admission, twenty-one had a value that was lower than or equal to 0.6 g/L. One of them had a fibrinogen

value between 0.7 and 1 g/L, and two had fibrinogens between 1 and 2 g/L. None of them had normal fibrinogen, higher than 2 g/L (***Table VII***).

Table VII: Initial Fibrinogen and Haemorrhagic Signs:

	Grade II																				Grade III		
N° Patient	2	3	5	6	7	8	10	14	15	16	17	18	19	22	24	25	26	27	28	29	30	1	9	23
Fibrinogen (N 2-4g/L) before immunotherapy	<0,6	<0,6	<0,6	0,8	<0,6	<0,6	<0,6	0,6	<0,6	<0,6	0,7	1,6	<0,6	0,6	0,6	<0,6	<0,6	<0,6	<0,6	<0,6	<0,6	1,7	0,6	0,6
Clinical haemorrhagic signs	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	No	Yes	No	No

Immunotherapy

Twenty-nine patients had grades higher than or equal to grade II. Therefore, immunotherapy was indicated for them. Twenty-six received at least one dose of immunotherapy. Three of them did not receive it due to stock shortages. Time between hospitalisation and antivenom injection was recorded for twenty-four patients (of the twenty-six who received the antivenom), and it varies from <1 hour to 17 hours.

1) Tolerance

No cases of severe anaphylactic reactions were reported after Antivipmyn-Tri® infusion.

Three patients had skin reactions. The first one was of the simple pruritus type, with good progress with antihistamines of the Polaramine type. The second one was urticaria. The third one was pruritus with rash. Therefore, the injection was discontinued, and treatment with antihistamines of the Polaramine type was started.

Patient 28 had an episode of vagal hypotension with spontaneous recovery and adequate blood pressure (BP) without adrenaline (the patient received Solumedrol and antihistamines pre-emptively).

2) Effectiveness

2.1. Clinical effectiveness

All patients who received immunotherapy showed stabilisation, and a subsequent regression of their oedema, as well as pain relief. An interruption of moderate haemorrhagic syndromes was also identified after immunotherapy.

No deaths were reported during this study.

2.2. Effectiveness on coagulopathy

All patients who received the serum showed a significant improvement of their PT and fibrinogen. PT and fibrinogen before and after immunotherapy were recorded for fourteen patients (***Table VIII***).

Table VIII: Coagulation Before and After Immunotherapy in Twelve Patients:

N° of patient	Before Immunotherapy		After Immunotherapy	
	PT (%)	Fibrinogen (g/L)	PT (%)	Fibrinogen (g/L)
3	21	<0,6	46	0,9
5	<10	<0,6	47	0,7
8	10	<0,6	39	1,3
14	44	0,6	54	2,6
15	<10	<0,6	55	2,7
17	20	<0,6	51	0,8
18	55	1,6	64	2,3
19	<10	0,7	59	3,8
23	<10	0,6	59	2,5
24	<10	0,6	56	1,5
25	20	<0,6	28	3,8
26	<10	<0,6	72	1,1
27	18	<0,6	87	2,4
28	17	<0,6	75	3,2

For the three patients who were prescribed immunotherapy but did not receive it, coagulation progress reports are variable (***Table IX***). Patient's 6 PT, which was initially close to the normal range became completely normal. In other patients, who had an initially negative report, an improvement without a normalisation was recorded.

Table IX: Evolution of Coagulation Parameters Without Immunotherapy:

	PT (%)	Fibrinogen
Patient 6		
H2	57	0,8
H48	72	*unknown*
Patient 7		
H6	<10	0,29
H48	50	1,4
Patient 22		
H6	<10	2,6
H63	56	0,7

Fibrinogen before and after immunotherapy was recorded for fourteen patients (***Table X***). We also have different dosages in two patients who were prescribed antivenom but did not receive it. In these patients, fibrinogen had not been normalised during the last reports, at least 48 hours after the bites. Among the patients who received the antivenom, eight normalised their fibrinogen (in at least 48 hours). Five patients who did not normalise their fibrinogen had an early balance at least 48 hours after the

bite, and their progress is unknown. The time of the last report of the last patient who did not normalise their fibrinogen is unknown.

Table X: Normalisation of Fibrinogen with and without VAS Injection:

N° Patient	Normalization of Fibrinogen	Blood test time (hours)
Patient without SAV Injection		
7	No	≥ 48H
22	No	≥ 48H
Patient with SAV Injection		
3	No	6H
5	No	24H
8	No	24H
14	Yes	≥ 48H
15	Yes	≥ 48H
17	No	29H
18	Yes	≥ 48H
19	Yes	≥ 48H
23	Yes	≥ 48H
24	No	*unknow*
25	Yes	≥ 48H
26	No	36H
27	Yes	≥ 48H
28	Yes	≥ 48H

Other Treatments

Frequent use of pre-emptive antibiotic Amoxicilline-Acide clavulanique (treatment prescribed at discharge) with or without identifying an infection. It is recorded in seven cases at least with a confirmed infection (abscess) and an increasing CRP, which indicates a biological inflammatory syndrome.

Two patients had to resort to surgery.

DISCUSSION

Epidemiology

There are no recent statistics on the annual incidence of snake bites in Saint Laurent du Maroni. It is therefore impossible to provide a comparison with the figures found which are, for 2015, twenty-one cases of patients suffering from envenomation admitted to hospital. This study provides important epidemiological data on snake bites in the region.

The time of year (rainy season), the times of day (peak at the end of the day) and the geographic location (forest) coincide with information found in literature (9). The bites were mainly accidental and affected the lower limb. Some of them could have been avoided by wearing shoes.

Among the snakes encountered and identified, two were *Bothrops brazili* and one was a *Lachesis muta*. All the other snakes seen were described as "lancehead". The so-called small-scaled lancehead is the *Bothrops brazili*; the large-scaled lancehead is the *Lachesis muta,* while the *Bothrops atrox* is also called "common lancehead" (8). The concept of "lancehead" is therefore different depending on the population and may correspond to all the species found in the region, apart from the *Micrurus*.

Initially, the identification of snake species was proposed in the criteria, however this poses challenges. The snake is rarely brought in for formal identification by experts, which means that its recognition depends on the patient's knowledge. There are therefore several snake species involved in the reported cases of envenomation, however it is impossible to draw conclusions regarding the distribution of species. This would require a formal identification, which could be done by bringing in the snakes in question, however the practice of doing so is rare and could be dangerous. Another type of identification can also be considered. It is possible to run a test which consists in swabbing the venom on the bite in order to obtain a venom sample as well as identify the species responsible. This would provide additional epidemiological data on the distribution of the species involved in cases of ophidian envenomation. The only definite conclusion we can reach is that snake bites in French Guiana usually involve *Crotalinae*.

The type of population and the work conducive to encounters between humans and snakes (and therefore envenomation) coincide with findings described in literature, namely a young working population (7). We found that the number of gold-washers is large in relation to the working environment. Children are also often affected when playing in green areas and forests.

All the snake bites treated at Saint Laurent du Maroni Hospital resulted in envenomation.

Lengths of hospitalisations were short, considering the clinical and biological examinations upon admission, with a median of 4 days. This should be compared with the lengths of hospitalisation prior to starting immunotherapy. The number of patients with grade II envenomation or higher, who did not receive antiserum, is too small in

this series (3 patients) to draw conclusions. Patient 1 was hospitalised the longest, i.e. for 34 days. The patient suffered from grade III envenomation, with a time between bite and hospitalisation of more than 12 hours, and received several doses of Antivipmyn-Tri®. There was a good improvement in general clinical and biological symptoms, however local complications such as necrosis required surgery three times: twice for debridement and once for a skin graft. Patient 25 also required a lengthy hospitalisation, extended to 28 days. The patient suffered from grade II envenomation, had local complications akin to an abscess at the site of the bite, and fluctuating coagulation test results with doubts regarding the administration of serum. Patients hospitalised longer than the mean length of hospitalisation suffered from serious local complications that required surgery.

The mean length of hospitalisation was higher for patients who were given immunotherapy with the longest delays. This length of hospitalisation is dependent on two factors: the time between bite and hospitalisation, and the time between hospitalisation and injection of antivenom. The first factor depends on the willingness of the victim to go to a healthcare centre, and the possibility for the victim to do so. As such, it can be improved by raising public awareness and improving the healthcare network in the country. The second factor depends on the hospital treatment and can therefore be reduced by continuing to improve the treatment protocol regarding snakebite envenomation and by training healthcare staff in the management of such situations. The length of hospitalisation is therefore correlated with both the time to hospitalisation and complications relating to the bite and the envenomation.

Some patients have been treated only in short-stay units and did not require hospitalization in a surgical department. It may be worth considering setting up short hospitalization branches in short-stay units for patients treated early and not showing any complications, with regular clinical and biological monitoring.

Clinical before Immunotherapy

Almost all patients admitted (twenty-nine of thirty) suffered from grade II or III envenomation with serious clinical symptoms. There were no dry bites reported in this study. Compared to vipers in France (close to a quarter of dry bites in a recent study) (47), it seems that snake bites in French Guiana most often cause envenomation. However, there is a recruitment bias due to the study site (the hospital) in a population that also has access to traditional medicine and where local healthcare centres exist.

Furthermore, we found that severity was also correlated with the speed at which treatment was provided. Indeed, all grade III patients can be found in the lower part of *Table IV*, with 4 grade III patients out of 5, with a time to antivenom injection higher than the average (15 hours).

The time between bite and injection is therefore long for all grade III patients, which confirms that the faster the injection, the less severe the envenomation (8,20).

There were no neurological symptoms observed during this study. The most common clinical symptoms were viper syndrome with extensive oedema.

Systemic symptoms were infrequent.

Among other factors, renal function was known for 21 of 30 cases, including 3 cases of acute renal failure. We are unaware of the progression of these. It seems that immunotherapy does not ensure initial improvement but impairment of renal function, although assessments were carried out very early and patients' medical history was not known. Changes in renal function and patients' initial state should be assessed. On the other hand, we know that the venom of certain snakes, such as *Crotalus durissus*, has a delayed nephrotoxicity. Even in cases where the *Crotalus durissus* has not been identified as the attacker, envenomation should be borne in mind as the potential cause of renal function impairment.

Coagulopathy before Immunotherapy

The biological chart is dominated by major haemostasis disorders which frequently occur in the event of envenomation by *Crotalinae* species found in the Americas (19). No patient had a normal PT or fibrinogen on arrival. Coagulation test results following envenomation were very low, with PT and fibrinogen levels sometimes unmeasurable. Sometimes associated with moderate haemorrhagic syndrome.

The most reliable reference parameter for coagulation is fibrinogen. It is more predictive of clinical severity because PT variation depends on several factors (49). Consequently, a study centred on the kinetics of coagulation, with a systematic dosage of fibrinogen, would be needed.

Immunotherapy

Antivenom administration was required for twenty-nine of thirty patients admitted. Twenty-six patients received at least one dose of immunotherapy, which was indicated for all of them. Its prescription is therefore justified.

Three patients with an indication for antivenom did not receive it due to stock shortage. In the case of the first two patients, this occurred during the first months after the serum was introduced, which can be explained by the fact that it was difficult to predict the amount of stock required at such an early stage. The third patient who did not receive serum was one among three cases of ophidian envenomation in the same week. Given that the envenomation occurred so close together, it was impossible to re-stock the antivenom in time to treat the last patient.

At least three patients received a second dose of antivenom. The first case occurred during the first instance of using the serum at the hospital; the patient received two doses on the same day due to slow improvement of biological symptoms. For the second case, the circumstances of the second injection are unknown. The third case involved secondary clinical and biological deterioration despite improvement following the first dose, probably because the serum's half-life had passed and the venom had recirculated.

Consequently, it is necessary to determine the criteria for administering further immunotherapy. It would require regular follow-up at fixed times, as detailed above, which would enable healthcare professionals to be aware of the reasons for the re-

administration of immunotherapy and therefore to reassess the dosage (number of vials) that should be administered initially.

This study did not report any serious allergic reactions apart from benign reactions with a favourable progression, which confirms the serum's safety, in accordance with known data. The only side effects reported were minor, cared for thanks to symptomatic treatment, and they did not justify the stopping of antivenom injection. In light of these minor side effects, the benefit-risk balance tips in favor of continuing immunotherapy.

The fast disappearance of clinical symptoms following immunotherapy confirms its effectiveness. In one case, oedema continued to spread and required a second dose of antivenom (correlated with further deterioration of coagulation parameters).

We found a significant improvement of coagulation parameters following immunotherapy. However, it is difficult to calculate precisely the mean time for coagulation parameters to become normal (inaccurate schedules, time difference, lack of schedule, early isolated tests). The cohort of patients with the indication for antivenom who did not receive it is too negligible to establish a reference and compare with the patients who did receive the serum.

To draw conclusions on the time for coagulation parameters to become normal (and therefore to compare with a potential cohort in the past), it would be necessary to carry out regular tests at H0, H6, H12, H24, H48 and H72. This is advocated in the protocol, but difficult to implement in practice. Changes in coagulation parameters, notably fibrinogen levels, seem to be favourable sooner following immunotherapy. *Table X* shows a return to normal fibrinogen levels during tests performed from 48 hours after envenomation in patients who received antivenom compared to patients who did not. Five patients who were given antivenom whose fibrinogen levels did not return to normal all underwent earlier tests. Consequently, we can assume that these figures could also return to normal at 48 hours. However, later tests (until normalisation) are lacking for patients who did not receive antivenom to compare with patients who did. It is important to note that hemostasis disorders evolve spontaneously towards a recovery in the span of one week (23).
The study's limitations lie in the fact that we do not have coagulation parameters for all patients, the requested parameters are not always the same before and after immunotherapy, and time to performing tests vary from one patient to the next. It is therefore difficult to establish precise figures.

No deaths were reported in this study. However, the Western France PCC was concerned with the death of a patient caused by ophidian envenomation in 2017 (Except for study because in Cayenne and not Saint Laurent du Maroni). The patient was thirty-nine years old and had no medical history. He was bitten on the foot by a "lancehead" in the morning. He was hospitalized for surveillance at the Cayenne Hospital Center with a reassuring clinical presentation. Then his condition deteriorated rapidly and he died in the night. He could not benefit from the antivenom. That caused a strong emotional response on the local population. This case highlights the severity of ophidian envenomations in French Guiana as well as the need to keep

improving the specific care of these envenomations. Following this, there was a more comprehensive need for antivenom in French Guiana.

Other treatments:

We found few infectious complications. Consideration should be given to the extent to which this can be attributed to frequent use of prophylactic antibiotic treatment (with Amoxicilline-Acide clavulanique) and determine the contributory factors in the event of identified infections (time between bite and hospitalisation, first treatment received on site) to prescribe a reasoned prophylactic antibiotic treatment.

The need for surgery was limited, with only two patients requiring it. The first patient suffered from grade III envenomation. The initial treatment was delayed, resulting in necrosis that required surgical debridement twice and a skin graft. The second patient suffered from grade II envenomation, but was treated for a local complication akin to an abscess.

The use of premedication such as antihistamines and corticoids was common and is not assessed in this study. As with antibiotic treatment, it would be interesting to assess it so that it can be recommended or discouraged.

The use of so-called traditional medicine (herbal remedies, healers, etc.) is common prior to hospitalisation, but has not been assessed in this study. Similarly, placing a tourniquet prior to hospitalisation has been referred to in some case, but is not assessed here.

Evolution/Outlook

1) Use the paraspecificity of venom antivenom

The development of antivenoms is currently focused on polyvalent serums by using the paraspecificity of serums. Paraspecificity (or cross-neutralisation) is the neutralising capacity of an antivenom for species other than the ones for which it was initially designed. Several examples can be found in literature (50,51,52).

However, the limitations of paraspecificity are linked to their effectiveness in the case of closely related ophidian species. Indeed, anti-Bothrops polyvalent antivenoms are effective in the event of envenomation by *Bothrops atrox* and b*razili* (study involving mice), however their paraspecificity is not sufficient for a satisfactory neutralisation of the venom of *Lachesis muta* (whose venom must be included in the product) (19). The effects of paraspecificity cannot be foreseen and must be checked from case to case (50). Furthermore, it is necessary to have reference materials, particularly on the evolution of biological parameters in the absence of serum to ensure that clinical and biological improvements are attributed to the non-specific serum and not to the natural progression of disorders (50).

However, the cross-reactivity of antibodies and antigenic components of venoms of different species offer hope for extensive use of these serums in cases of envenomation by species not used in the making of antivenoms (46).

2) Standardise treatment for envenomations in Guiana:

Implementing a national strategy relating to fight against envenomation would improve their treatment. The recommendations found in the *WHO Guidelines for the Management of Snakebites* (27) advocate including training on snakebites in medical studies. Ultimately, the goal of this strategy is to standardise treatment across French Guiana in accordance with WHO guidelines, improve the training of medical and paramedical staff, raise public awareness, and continue with the gathering of epidemiological data and clinical and biological knowledge to ensure better decision-making regarding public health.

To achieve this goal, consideration could be given to simplifying the existing protocol and circulating it among all the healthcare institutions in the country. Although highly exhaustive, the protocol includes several volumes and is perhaps too long to be used in everyday practice. We could therefore summarise on one page the main clinical and biological elements and simplify the monitoring sheet. A more comprehensive document corresponding to the current protocol would be available in relevant services (namely emergency, resuscitation and surgical departments).

Limitations

The primary limitations of this study are those inherent in the use of prospective data and PCC records. Information was collected over the phone and recorded by a specialist in the Poison Control Centre. Patient records from Saint Laurent du Maroni Hospital could not be reviewed, and we only had access to PCC data, occasionally supplemented by additional data sent by the hospital. Although the PCC clinical toxicologist offered recommendations, the final decisions to treat patients with one or more doses of Antivipmyn-Tri® or to initiate other symptomatic treatments (corticosteroids, antibiotics) were taken by the emergency physician.

Other limitations include long-term sequelae which could not be assessed given that patient follow-up at D15 could not be carried out in most cases. This also applies to the serum's delayed side effects, such as serum sickness.

To date, there is no comparison of these parameters with cases treated systematically prior to serum administration.

CONCLUSION

Ophidian envenomation in French Guiana is non-negligible and can be life-threatening. Passive immunotherapy is the specific standard treatment. Antivipmyn-Tri® is currently the only effective antivenom to treat venomous bites from French Guiana snakes. It is both effective and well-tolerated. Its introduction at Saint Laurent du Maroni Hospital resulted in the improvement of ophidian envenomation treatment thanks to shorter lengths of hospitalization, fast improvements on clinical and biological symptoms (notably coagulation parameters), a rare need for surgery and few side effects attributable to the product.

In the future, it is vital to propose standardised methods of treatment across French Guiana. To this end, it is necessary to continue with the assessment of current immunotherapy with Antivipmyn-Tri® for tolerance and effectiveness. Every hospital structure in French Guiana would have to work towards this objective as following this experiment. The decision to generalize the use of the antivenom in all French Guiana was taken by the local authorities.

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LISTE DES TABLEAUX

TABLE DES MATIERES

ANNEXE :

Protocole de prise en charge des envenimations ophidiennes hors Micrurus au centre hospitalier de Saint Laurent du Maroni.

RECOMMANDATION DE PRISE EN CHARGE DES ENVENIMATIONS OPHIDIENNES.

(hors Micrurus)

SYSTEMATIQUEMENT REMPLIR LA FICHE RENSEIGNEMENT (page 3 et 4) **A REMETTRE A LA PHARMACIE**

Evaluation du terrain : mode de vie / ATCD médico-chirurgicaux / allergie / traitements habituels
Terrain à risque = enfant / personne âgée / grossesse (surmortalité fœtale)

CLINIQUE : la morsure

Où ? (« exemple : forêt, proche de la crique machin .... »)
Quand ? (jour / heure)
Comment ? (« marché dessus » / « manipulation » ....)
Par quoi ? Taille - aspect du serpent-identification photo
Descriptif de la lésion :

- Nombre de traces de crochets
- Distance entre les 2 crochets
- Site de(s) morsure (s)
- Signes locaux : phlyctènes ? saignements ?
- Signes régionaux : œdème ? phlyctènes ...
- Signes généraux

Examen complet dont ECG & examen neuro détaillé
(N. crâniens, ptosis, ROT, acouphènes, diplopie ...)

1

La biologie : NFS, plaquettes, TP, TCA, fibrinogène, urée, créatininémie

Dans tous les cas *(hors défaillance vitale)*

. Calmer / rassurer le patient
. Oter bagues, bijoux... pouvant bloquer la circulation
. Déshabiller (couper vêtements du segment concerné)
. Traitement local (désinfection de la plaie à la bétadine x3/j)
. Antalgie (CI aux traitements anticoagulants types AINS ....)
. Antibioprophylaxie (amox-clavu de 1° intention hors CI)
. Vérifier le statut vaccinal antitétanique et SAT/VAT si nécessaire
. Immobilisation par bandage lâche, position fonctionnelle
. Surélévation du membre

GRADE D'ENVENIMATION

Grade	SIGNES CLINIQUES (un critère au moins définit le grade)			SIGNES BIOLOGIQUES (un critère au moins définit le grade)
	Syndrome vipérin	Signes généraux	Syndrome neurotoxique	
0	- Douleur modérée, traces de crochets. - Pas œdème. - Pas hémorragie.	aucun	aucun	aucun
1	- Douleur marquée. -Œdème ne dépassant pas l'articulation sus jacente. - Pas hémorragie.	aucun	aucun	=> **Troubles mineurs de l'hémostase :** - 80Giga/L<Plaquettes < 150Giga/L - 45%<TP<70% - 1g/L<fibrinogène<2g/L
2	- Œdème dépassant l'articulation sus jacente. - Phlyctène(s), nécrose mineure. - Saignement modéré au niveau de la morsure, hématurie, gingivorragie.	- Signes digestifs (diarrhée, vomissements, douleur abdominale). - Signes hémodynamiques (tachycardie, hypotension). - Douleur thoracique.	Ptosis, diplopie, mydriase, trouble de la déglutition, syndrome myasthéniforme, fasciculations, myalgie, paralysie flasque	=> **Coagulopathie :** - Plaquettes<80Giga/L - TP<45%-TCAx2 - Fibrinogène <1g/L => **Insuffisance Rénale aigue :** Créatinine > 120µmol/L => **Rhabdomyolyse :** CPK 1000UI/l
3	- Œdème atteignant ou dépassant la racine du membre, nécrose étendue. - Hémorragie grave (épistaxis, hémoptysie, saignement digestif)	Etat de choc.	Détresse respiratoire.	**Coagulopathie** et **Hb<9g/dL**
		Coma, Convulsion.		

2

⇨ Grade supérieur si : - grossesse
- âge<11ans ou >60ans
- poids corporel<25kg
- localisation de la morsure visage ou cou

Grade de l'envenimation	Conduite à tenir
Grade 0	- Surveillance 6h à l'hôpital.
Grade 1	- Surveillance 24h à l'hôpital. - Bilan biologique toutes les 6h.
Grade 2	- SERUM ANTI-VENIMEUX le plus précocement - Bilan biologique 6 à 12h après le sérum antivenimeux.
Grade 3	

3

Mettre en place la FEUILLE DE SURVEILLANCE p.4

Voir PROTOCOLE SERUM ANTI-VENIMEUX p.5

RECOMMANDATION DE PRISE EN CHARGE DES ENVENIMATIONS OPHIDIENNES.

CONDUITE A TENIR

⇨ Traitement symptomatique :

- Soins locaux simples (désinfection)
- PAS de corticoïde, PAS d'HBPM ni HNF (aggravent l'hématome et allongent la durée d'hospitalisation).
- Antibioprophylaxie par AUGEMNTIN en 1ère intention en l'absence de CI.
- Surveillance horaire de l'extension de l'œdème vers un grade II.

⇨ Antalgiques : Palier 1 ou 2.

⇨ Sérum anti venimeux : ANTIVIPMYN-TRI® : indiqué dès le grade II.

- Le plus précoce possible (idéalement dans les 6 premières heures) pour une efficacité optimale, mais possible jusqu'à 36h après la morsure.
- 1 dose soit 3 ampoules, même posologie pour adultes/enfants/femmes enceintes.
- Perfusion des 3 ampoules dans 125ml de sérum physiologique chez l'adulte et 60ml de sérum physiologique chez l'enfant, sur 1 heure.
- Patient à jeun pour 8 heures.
- Dépister des signes d'intolérance immédiate : rash cutané, malaise, hypotension…

⇨ Si suspicion de thrombose veineuse profonde du membre mordu :

Echo-doppler veineux et traitement de la thrombose veineuse profonde si nécessaire.

⇨ Suivi à J15 du patient: PREVOIR UN CONTACT TELEPHONIQUE AVEC LE PATIENT OU UN TIERS

Recherche de signes de maladie sérique.

Recherche d'une gêne fonctionnelle persistante.

RECOMMANDATION DE PRISE EN CHARGE DES ENVENIMATIONS OPHIDIENNES.

Fiche de renseignement patient à l'admission- A remettre à la pharmacie

A remplir **systématiquement**, qu'un sérum antivenimeux soit administré, **ou non**

ETIQUETTE PATIENT

	Date	Heure
Entrée à l'hôpital	___/___/_____	
Sortie définitive de l'hôpital	___/___/_____	

EVENEMENTS

- Localisation géographique du lieu de l'envenimation : .....
- Circonstances de l'accident : .....
- Eléments descriptifs du serpent (taille, couleur, aspect ...) .....

Contact téléphonique pour le suivi : .....

Cocher ☐ serpent mort ramené par le patient (à conserver au SAU, récipient portant l'étiquette du patient)

Et signaler par mail le cas à l'expert pour identification du serpent: Mr F. STARACE fausto.snake@hotmail.fr ou adresser la photo au CAP d'Angers : cap49@chu-angers.fr

TERRAIN

Allergie connue ? .....

ATCD médico-chirurgicaux ? .....

Traitement habituel ? .....

.....

- Grossesse ? .....

- Traitement pris le jour de l'accident ?.....

.....

ETAT CLINIQUE à l'ADMISSION

pouls *TA* *FR* *Sp02*(AA) *Glasgow*

- **Douleur** ☐ absente ☐ modérée (pallier 1 suffit) ☐ marquée (pallier 2 ou plus)
- **Œdème** ☐ absent ☐ < articulation sus jacente ☐ < racine de membre ☐ ≥ racine de membre
- **Nécrose** ☐ absente ☐ mineure ☐ étendue
- **Saignement** ☐ absent ☐ modéré ☐ grave
- **Phlyctène(s) :** ☐ ☐
- **Signes neuro d'alerte :** ☐ ☐ - **Signes digestif :** ☐ ☐ - **Douleur thorax :** OUI ☐ NON ☐
- **Détresse respiratoire :** OUI ☐ NON ☐ - **Etat de Choc :** OUI ☐ NON ☐ - **Coma, Convulsion :** OUI ☐ NON ☐

BIOLOGIE à l'ADMISSION

Hémoglobine ..... Plaquettes ..... Urée..... Créatininémie.....

TP..... TCA..... Fibrinogène.....

Grade d'envenimation retenu (0 à 3) : .....

Si grade ≥ 2 : débuter protocole « SERUM ANTI-VENIMEUX : ANTIVIPMYN® »(page 4)

1 **Demande faite** au centre 15 & CAP Angers ☐ OUI ☐ NON

2 **Décision** ..... ☐ proposer le sérum ☐ ne pas proposer le sérum

TRAITEMENTS EFFECTUES AUX URGENCES

Nom du sérum :
Date et Heure de la 1ère administration: .....
2ème dose : ☐ oui ☐ non Si oui date et heure :.....
Nombre total d'ampoule(s) délivrée(s) : .....
Signes d'intolérance : ☐ oui ☐ non Préciser: .....

SUIVI TARDIF

SUIVI TELEPHONIQUE A J15	
Gêne fonctionnelle persistante	☐ oui Préciser : ..... ☐ non
Signes locaux	Préciser : .....
Maladie sérique	Fièvre ☐ Eruption cutanée ☐ Polyarthralgies ☐ Adénopathies ☐ Autres☐
Signes biologiques à rechercher si signes cliniques présents	↑ VS ☐ Protéinurie ☐ Hématurie ☐ ↓ C3 ☐ ↓ C4 ☐ Immuncomplexes circulants à IgM et IgG ☐
Consultation médicale	☐ oui ☐ non si oui Traitement prescrit : .....

ETIQUETTE PATIENT

PROTOCOLE PRISE EN CHARGE DES ENVENIMATIONS OPHIDIENNES

Feuille de Surveillance

A photocopier et transmettre à la pharmacie lors de la clôture du dossier

Date et heure de l'envenimation : .....

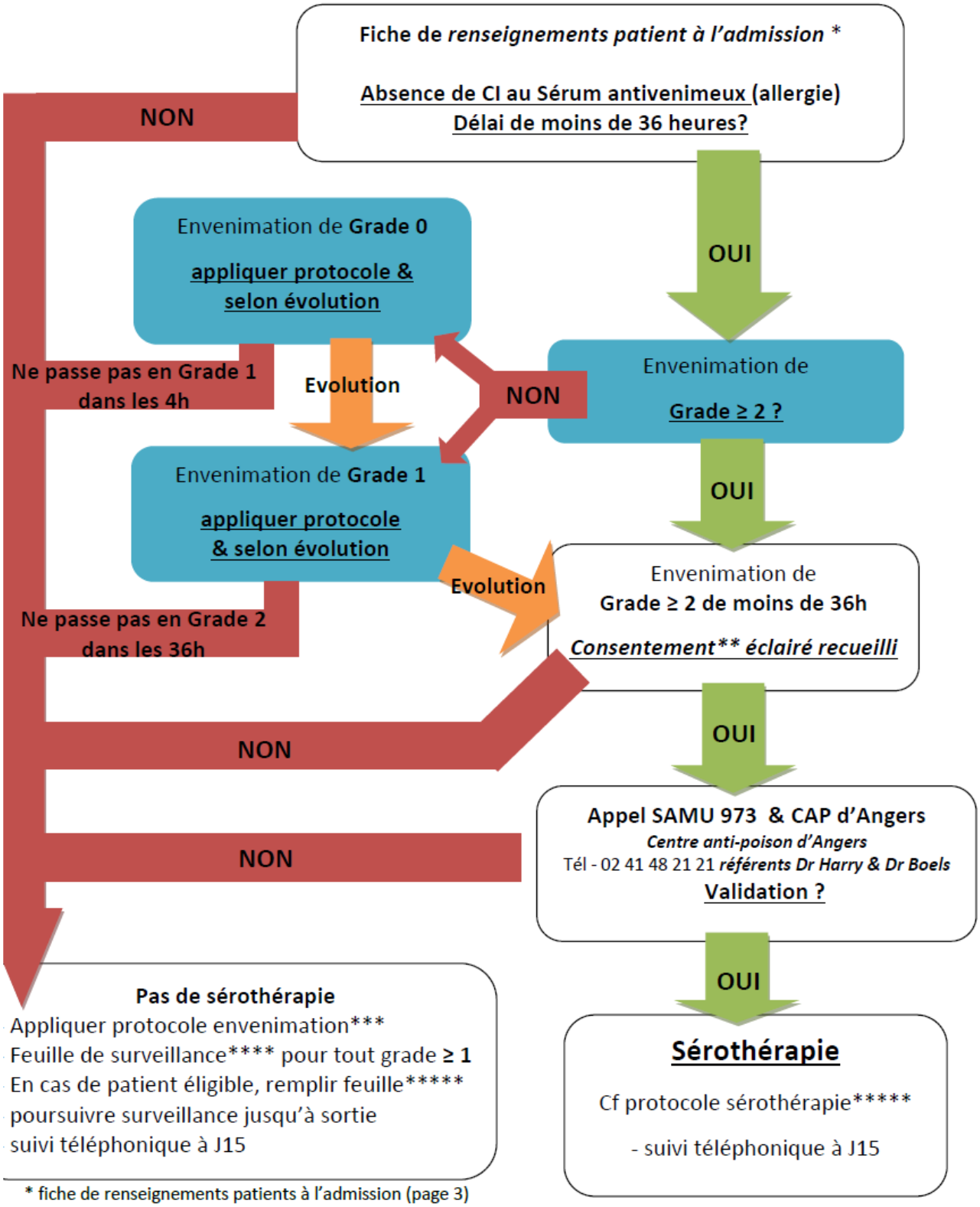
Date et heure de la première évaluation : .....

Délai en heure entre envenimation et première évaluation : .....

* 0 = absente ou modérée (recours aux pallier 1) / 1 = douleur marquée (pallier 2 ou 3)
** 0 = absence / 1 = < coude - genou / 2 = <racine de membre / 3 = ≥ racine d'un membre
*** 0 = absente / 2 = mineure / 3 = étendue
**** 0 = absent / 2 = modéré (niveau morsure - point de ponction - hématurie - gingivorragie) / 3 = grave (épistaxis - hémoptysie - hémorragie digestive)

GRIS : Faire photos sur accord du patient / adresser cliché par voie de mail, avec 3 premières lettres du nom / prénom & date à v.lambert@ch-ouestguyane.fr

	Délai envenimation/admission / Paramètre	H0	H6	H12	H18	H24	H30	H36	H48 /J2	H60	H72 /J3	J4	J5	J6	J7
Clinique	Pouls (/min)														
	TA (Pas/Pad)														
	FR (/min)/ Sp02 AA (%)														
	Glasgow (3 à 15)														
	Douleur*														
	Œdème**														
	Nécrose***														
	Phlyctène (+/-)														
	Saignement****														
	s.neuro d'appel (+/-)														
	s. digestifs (+/-)														
	douleur thoracique (+/-)														
	détresse respiratoire (+/-)														
	etat de choc (+/-)														
	coma/convulsion (+/-)														
Biologique	Hb (g/dL)														
	Plaquettes (/mm3)														
	Créatininémie (µmol/L)														
	TP (%)														
	TCA (rapport)														
	Fibrinogène (g/L)														
Grade de l'envenimation (0 à 3)															
Nombre de flacons de sérum injectés															



* fiche de renseignements patients à l'admission (page 3)
** Consentement éclairé du patient ou de son représentant légal (page 6)
*** Protocole prise en charge envenimation ophidienne (page 1)
**** Feuille de surveillance (page 4)
***** Protocole administration de la sérothérapie (page 8)

Recherche du consentement éclairé du patient ou de son représentant légal

Fiche à transmettre à la pharmacie, quelle que soit la décision du patient

Nom et prénom (Mme, Mlle, M.) : .....

Né(e) le : .....

Lors de la consultation du (date) : .....

Je me suis entretenu avec le Dr : .....

Concernant l'administration du sérum anti-venimeux ANTIVIPMYN®

Il m'a donné des informations précises sur mes problèmes de santé, leurs raisons et leurs risques évolutifs, le conduisant à me proposer l'administration de ce produit.

J'ai également reçu toutes les informations sur les risques de l'intervention proposée, les bénéfices attendus et le différentes alternatives thérapeutiques possibles.

J'ai compris qu'il existe un risque de réaction allergique pouvant mettre en jeu mon pronostic vital.

Je reconnais que le praticien a répondu de façon complète et compréhensible à toutes les questions que j'ai souhaité lui poser.

J'ai disposé d'un délai suffisant de réflexion et je : donne mon accord pour cet acte ..... ☐

Refuse de recevoir ce produit ..... ☐

Fait à : .....

Le : .....

Signature du praticien : Signature du patient :

RECOMMANDATION DE PRISE EN CHARGE DES ENVENIMATIONS OPHIDIENNES.

Protocole d'administration de la sérothérapie *ANTIVIPMYN®* **Page 7**

à adresser à la pharmacie
document faisant fonction d'ordonnance

ETIQUETTE PATIENT

COCHER pour valider

1° - Absence de contre-indication connue pour le patient ..... ☐

2° - Patient éligible (Grade ≥ 2 & envenimation de moins de 36h)..... ☐

3° - Consentement éclairé du patient obtenu (papier signé) ..... ☐

4° - Accord du Centre 15 et du CAP d'Angers obtenu ..... ☐

En cas de refus, expliquer les raisons de celui-ci : .....

.....

.....

Fournir les 3 à 4 documents exigibles (cf. infra) à la pharmacie qui délivre **3 ampoules d'**antivipmyn tri (de nuit, appeler le pharmacien de garde).

Administration : ***une fois l'indication posée , elle doit se faire aussi précocement que possible***

- Patient mis à jeûn pour 8 heures
- ***Sous surveillance continue, au déchoquage, jusqu'à 24h après l'administration*** (avec relevés sur feuille de surveillance *(protocole prise en charge des envenimations ophidiennes)*)
- Administration de **3 ampoules**

Sauf posologie différente déterminée lors de la conférence téléphonique SAU / SAMU / CAP Angers

  - Diluée dans du NaCL 0,9% (sérum salé isotonique) : 125 mL chez l'adulte et 60 mL chez l'enfant
  - Par voie intra-veineuse sur 1 heure

Une nouvelle dose peut être réadministrée, à H6 : selon l'évolution, et après discussion et accord collégial avec le centre 15 et le CAP d'Angers

Fait à Saint-Laurent-du-Maroni, le : .....

Docteur : .....

Signature :

Adresser à la pharmacie un exemplaire de :
(& on garde une photocopie LISIBLE de chacun dans le dossier)

. La fiche de renseignement patient à l'admission (protocole prise en charge des envenimations ophidiennes) (*page 2*)

. La feuille de consentement éclairé du patient, signée (*page 5*)

. La feuille de surveillance (protocole prise en charge des envenimations ophidiennes) (*page 3*)

- Lorsque l'indication de sérothérapie est posée en cours de surveillance (dans ce cas la feuille est exigée pour remettre le traitement)
- Lors de la clôture du dossier du patient

. Ce protocole d'administration de sérothérapie signé par le médecin

NADAUD Alice

Envenimations ophidiennes en Guyane française : première évaluation clinique d'un nouveau sérum antivenimeux.

RÉSUMÉ

Introduction

L'envenimation ophidienne en Guyane française est potentiellement grave, car elle peut mettre en jeu le pronostic vital et peut provoquer des séquelles fonctionnelles sur le membre mordu. L'immunothérapie est le traitement spécifique de référence mais il n'était pas disponible sur le territoire. En novembre 2014, une collaboration entre l'Hôpital Saint-Laurent-du-Maroni et le Centre antipoison de l'Ouest de la France (CAP) a permis la mise en place d'un protocole afin de traiter efficacement les cas d'envenimation. Un stock d'antivenin Antivipmyn-Tri® a été mis à disposition. Le but de cette étude est d'évaluer la tolérance et l'efficacité de l'immunothérapie Antivipmyn-Tri®, ainsi que de recueillir des données épidémiologiques sur les patients envenimés à Saint Laurent du Maroni afin d'améliorer le traitement de l'envenimation ophidienne dans toute la région.

Méthodes

Cette étude prospective et observationnelle inclut tous les cas d'envenimations ophidiennes par *Crotalinae* - entre novembre 2014 et juin 2016 - admis à l'hôpital de Saint-Laurent-du-Maroni et ayant donné lieu à un avis auprès du CAP de l'Ouest de la France.

Résultats

Trente cas d'envenimation ophidienne ont été recensés. L'envenimation concernait principalement les sujets masculins (77%), entre 15 et 65 ans (73%, avec une moyenne à 36 ans), surtout pendant la saison des pluies, pendant le travail ou les déplacements en forêt à la fin de la journée. Les circonstances sont principalement accidentelles et les morsures de serpent sont situées sur le membre inférieur. La gravité finale a été divisée en 0 grade 0, 1 grade I, 24 grade II et 5 grade III. L'hospitalisation a duré en moyenne 6 jours. 26 patients qui ont reçu Antivipmyn-Tri® ont montré une stabilisation et une régression de leurs signes cliniques avec une amélioration significative, voir une normalisation, de leur TP et de leur fibrinogène. Aucun cas de réaction anaphylactique sévère et aucun décès n'a été rapporté au cours de cette étude.

Conclusion

Antivipmyn-Tri® est actuellement le seul antivenin pour la prise en charge des envenimations par des serpents guyanais. Il est à la fois efficace et bien toléré.

À l'avenir, il est essentiel de proposer une prise en charge standardisée dans toute la région de la Guyane française. Pour cela, il est nécessaire de continuer à évaluer l'immunothérapie actuelle par Antivipmyn-Tri®, au niveau de la tolérance et de l'efficacité.

Mots-clés : Guyane Française, Sérum antivenimeux, Serpent, Antivipmyn-Tri®, Envenimation ophidienne.

Snake envenomings in French Guiana : first clinical assessment of a new antivenom.

ABSTRACT

Introduction
Ophidian envenomation in French Guiana is a potentially severe matter, as it can be life-threatening and can cause functional after-effects on the bitten limb. Immunotherapy is the specific reference treatment but it was not available on the territory. In November 2014, a collaboration between the Saint Laurent du Maroni Hospital and the Western France Poison Control Center (PCC) set up a protocol in order to efficiently treat envenomation cases. A stock of Antivipmyn-Tri® antivenom was made available. The purpose of this study is to assess the tolerability and efficacy of immunotherapy using the Antivipmyn-Tri®, as well as gather epidemiological data on envenomed patients in Saint Laurent du Maroni in order to improve treatment of ophidian envenomation in the whole region.

Methods
This prospective and observational study includes all *Crotalinae* related ophidian envenomation cases - between November 2014 and June 2016 - admitted to the Saint Laurent du Maroni Hospital and that required advice from the Western France PCC.

Results
Thirty envenomation cases were counted. Envenomation mainly concerned male subjects (77%), between 15 and 65 years old (73%, averaging 36 years old), mostly in rainy season, during work or a walk in the forest at the end of the day. The circumstances are mainly accidental and snakebites are located in the lower limb. The final severity was divided into 0 grade 0, 1 grade I, 24 grades II and 5 grades III. The hospitalization lasted on average of 6 days. 26 patients who received Antivipmyn-Tri® showed stabilisation and a regression of their clinical signs along with a significant improvement, often standardization, of their PT and fibrinogen. No cases of severe anaphylactic reactions and no deaths were reported during this study.

Conclusion
Antivipmyn-Tri® is currently the only effective antivenom able to treat venomous bites from French Guiana snakes. It is both effective and well-tolerated.
In the future, it is of vital importance to offer standardised treatment methods across the whole French Guiana region. To this end, it is necessary to keep assessing the current immunotherapy that uses Antivipmyn-Tri®, for tolerance and effectiveness.

Keywords: French Guiana, Antivenoms, Snake, Antivipmyn-Tri®, Envenomation.