Pit Vipers: From Fang to Needle—Three Critical Concepts for Clinicians

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Disclosures / Potential Conflicts of Interest

• Keith Boesen and Nicholas Hurst are employed by Rare Disease Therapeutics, Inc. (RDT)

• RDT is a U.S. company working with Laboratorios Silanes, S.A. de C.V., a company in Mexico

• Laboratorios Silanes manufactures a variety of antivenoms

Note: This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.
Learning Objectives

At the end of this session, participants should be able to:

1. Describe the venom variability in North American Pit Vipers
2. Evaluate the clinical symptoms associated with a North American Pit Viper envenomation
3. Develop a treatment plan for a North American Pit Viper envenomation
My level of expertise in treating Pit Viper Envenomation is...

a. I wouldn’t know where to begin!
b. I have seen a few cases...
c. I know a thing or two because I’ve seen a thing or two
d. I frequently treat these patients
e. When it comes to Pit Viper envenomation, I am a Ssssuper Sssskilled Ssssnakebite Sssspecialist!!!
PIT VIPER ENVENOMATIONS
PIT VIPERS

Loreal Pits

Movable Fangs

1. Russel 1983 - Photo provided by the Arizona Poison and Drug Information Center
PIT VIPERS

Loreal Pits

Movable Fangs

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PIT VIPERS

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Movable Fangs

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PHYLOGENETIC TREE

Serpentes
Viperidae
Elapidae
Crotalinae
Crotalus
Sistrurus
Agkistrodon
Pit Vipers

2. Venombyte 2019
-Photos provided by the Arizona Poison and Drug Information Center
**EPIDEMIOLOGY**

- **U.S. Species and Subspecies = 39**
  - *Agkistrodon* = 8
    - Copperhead, Cottonmouth/Water Moccasin
  - *Sistrurus* = 6
    - Pygmy, Massasauga
  - *Crotalus* = 25
    - Rattlesnake

- **Envenomations by Pit Vipers**
  - U.S. Estimates: >6,000
  - AAPCC: 4,183 in 2019
  - Outcome Major: 171
  - Death: 1
TRUE or FALSE: The exact species of Pit Viper must be known in order to determine the correct treatment for a patient who has been bitten.

a. True
b. False
VENOMICS
VENOMICS

- Phospholipase A$_2$ - Hemolysis/Myotoxic/Neurotoxic
- SVSP - Coagulopathy/Edema/Hypotension
- SVMP - Coagulopathic/Hemorrhagic/Myonecrosis
- L-amino acid oxidase - Cytotoxic/Myotoxic
- Cysteine-Rich Secretory Proteins - Smooth Muscle Paralysis
- C-Type Lectins - Thrombocytopenia
- Disintegrins - Inhibition of Platelet Aggregation
- Peptides - Hypotension/Myotoxic
VENOMICS

- Phospholipase A₂ - Hemolysis/Myotoxic/Neurotoxic
- SVSP - Coagulopathy/Edema/Hypotension
- SVMP - Coagulopathic/Hemorrhagic/Myonecrosis

CROTALINE (65 SPECIES)
VENOMICS

SPECIES TO SPECIES VARIATION

-Photo provided by RDT
FOUR GENERA OF PIT VIPERS

Crotalus (10 species)

Bothrops (10 species)

Agkistrodon (3 species)

Lachesis (4 species)

- PLA$_2$
- SVSP
- SVMP
- LAAO
- CRiSP
- CTL
- DIS
- NP
- VEGF
- DEF
- Mpi
- MVC
VENOMICS

INTRASPECIES VARIATION

-Photo provided by RDT
Mohave Rattlesnake
(*Crotalus scutulatus*)

-Photo provided by the Arizona Poison and Drug Information Center
VENOMICS

ONTogenic VARIATION

-Photo provided by RDT
VENOMICS

- **C. atrox**
  - Juveniles > hemorrhagic toxins than Adults

- **C. simus**
  - Newborn = Crotoxin
  - Juvenile = Less Crotoxin
  - Adult = Almost no Crotoxin

- **B. asper**
  - Newborn > Hemorrhagic
  - Adults > Myotoxic

- Similar findings with *Crotalus godmani* and *Atropoides mexicanus*

All of the following are potential signs or symptoms of envenomation by a North American Pit Viper EXCEPT:

a. Pain
b. Nausea, vomiting, and diarrhea
c. Transient global amnesia
d. Muscle twitching/fasciculations
CLINICAL EFFECTS
CLINICAL PRESENTATION

LOCAL

- Puncture wound(s)
- Pain
- Progressive swelling/edema
- Bruising
- Swelling in lymph nodes
- Local necrosis
- Blebs and bullae
- Muscle breakdown

-Photos provided by the Arizona Poison and Drug Information Center
CLINICAL PRESENTATION

HEMATOLOGIC

- Ecchymosis, bruising
- Decrease platelets
- Decrease fibrinogen
- Prolonged PT/INR
- Prolonged PTT
- Positive fibrin split products

-Photo provided by the Arizona Poison and Drug Information Center
CLINICAL PRESENTATION

SYSTEMIC

- Nausea, vomiting, diarrhea
- Weakness
- Muscle fasciculations
- Angioedema
- Laryngeal edema
- Signs of Shock
TREATMENT
**PRE-HOSPITAL**

**DO NOT**
- Capture the Snake
- Cut and Suck
- Snakebite Kits
- Tourniquets
- Constrictive bands
- Splint
- Cryotherapy
- Electricity

**DO**
- Transportation to Healthcare Facility ASAP
- Use Cell Phone
- Use Car Keys
HOSPITAL

ABCs

• History
• Physical Exam
• Measurement of Vital Signs
• Palpation of the envenomated area
• Marking the leading edge of swelling and tenderness (q15-30m)
• Elevation of the envenomated extremity
  – As high as possible/comfortable
  – As straight as possible
• Pain Medications
  – Opioids
  – Avoid NSAIDs
• Notify Poison Center (800-222-1222)

Signs of Envenomation

• Local Injury
  – Progressive Swelling (more than minimal)
  – Tenderness
  – Redness
  – Ecchymosis
  – Blebs at bite site
• Hematologic
  – Elevated PT
  – Decreased Platelets/Fibrinogen
• Systemic Signs
  – Hypotension
  – Vomiting
  – Angioedema
  – Neurotoxicity
ANTIVENOM
Audience Poll Question: #4 of 5

When the decision to treat an envenomated patient with antivenom is made, how many loading doses should be given?

a. Only one loading dose is necessary
b. A maximum of 2 doses
c. A maximum of 3 doses
d. As much as it takes
ANTIVENOM

Venoms → Immunize → Host Animal → Extract → Plasma → Antibody → Cleave → Remove Fc Portion

13. Lausten 2018
ANTIVENOM

- Bothrops asper
- Crotalus simus

- Crotalus atrox
- C. adamanteus
- C. scutulatus
- Agkistrodon piscivorous

There have only been five prospective trials conducted with Pit Viper antivenom in the United States.
PROSPECTIVE ANTIVENOM RESEARCH

1997

Fab Rattlesnakes
N = 11

2001

Fab Rattlesnakes
N = 31

2013

F(ab')2 vs Fab Rattlesnakes
N = 12

2015

F(ab')2 vs Fab All Pit Vipers
N = 114

2017

Fab Copperheads
N = 74

Affinity-Purified, Mixed Monospecific Crotalid Antivenom Ovine Fab for the Treatment of Crotalid Venom Poisoning.
- All 11 patients had a beneficial response.
- 10 out of 11 patients recovered with 4 or 8 vials
- Fab halted the progression of envenomation. Initial safety data was promising.

A Randomized Multicenter Trial of Crotalinae Polyvalent Immune Fab (Ovine) Antivenom for the Treatment for Crotaline Snakebite in the United States.
- 15 patients: single dose Fab with scheduled doses
- 16 patients: single dose Fab with PRN doses
- Fab effectively terminated venom effects
- Treatment regimen may require more than 1 dose
Subacute coagulopathy in a randomized, comparative trial of Fab and F(ab’)₂ antivenoms
• 12 patients (6 Fab and 6 F(ab’)₂)
• Acute Phase = All Venom Neutralized
• Sub-Acute Phase = Fab patients were more likely to experience late coagulopathies while F(ab’)₂ recipients did not.

Comparison of F(ab’)₂ versus Fab antivenom for pit viper envenomation: A prospective, blinded, multicenter, randomized clinical trial.
• 114 (39 Fab and 77 F(ab’)₂)
• Late Coagulopathies: Fab 29.7% and F(ab’)₂ 7.8%
• F(ab’)₂ reduced the risk of subacute coagulopathy and bleeding
The Efficacy of Crotalidae Polyvalent Immune Fab (Ovine) Antivenom versus Placebo Plus Optional Rescue Therapy on Recovery from Copperhead Snake Envenomation: A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial.

- 74 patients (45 Fab, 29 Placebo)
- Treatment with Fab reduces limb disability measured by the Patient-Specific Functional Scale 14 days after Copperhead envenomation.
COURSE OF TREATMENT

Assess Patient

Signs of Envenomation

Indications for Antivenom

Antivenom

Dose(s)

Initial Control

Observe

PRN Dose(s)

Discharge Criteria

Discharge Planning

Follow Up

### COURSE OF TREATMENT

<table>
<thead>
<tr>
<th>Assess Patient</th>
<th>Signs of Envenomation</th>
<th>Indications for Antivenom</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F(ab’)₂</strong></td>
<td>Dose</td>
<td>Initial Control</td>
</tr>
<tr>
<td><strong>Fab</strong></td>
<td>Dose</td>
<td>Initial Control</td>
</tr>
</tbody>
</table>

**Discharge Criteria**

**Discharge Planning**

**Follow Up**

COURSE OF TREATMENT

Assess Patient

Signs of Envenomation

Indications for Antivenom

F(ab')2

10 vials

Initial Control

Obs 18hr

4 vial PRN

Fab

4-6-12 vials

Initial Control

2vials q6hr x3

2 vial PRN

Discharge Criteria

Discharge Planning

Follow Up

## PRODUCT COMPARISON PER PACKAGE INSERTS

<table>
<thead>
<tr>
<th><strong>Dosing</strong></th>
<th>F((\text{ab}'))_2</th>
<th>Fab</th>
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</thead>
<tbody>
<tr>
<td>Stabilizing Dose (Vials)</td>
<td>10</td>
<td>4-6-12</td>
</tr>
<tr>
<td>Maintenance Dose</td>
<td>None</td>
<td>2 vials q6h x3</td>
</tr>
<tr>
<td>Observation Time</td>
<td>18 hours</td>
<td>18 hours</td>
</tr>
<tr>
<td>PRN AV (during observation)</td>
<td>4 vials</td>
<td>2 vials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pharmacy</strong></th>
<th>F((\text{ab}'))_2</th>
<th>Fab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstitution Time</td>
<td>11.8 sec (average)</td>
<td>No Mention</td>
</tr>
<tr>
<td>Stability after Reconstitution</td>
<td>6 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td>Storage</td>
<td>Room Temperature</td>
<td>Refrigeration</td>
</tr>
<tr>
<td>Half-Life</td>
<td>133 hours</td>
<td>15 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Efficacy</strong></th>
<th>F((\text{ab}'))_2</th>
<th>Fab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Control</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>Late Coagulopathy</td>
<td>7.8%</td>
<td>50%</td>
</tr>
</tbody>
</table>

SUMMARY

• Pit Vipers share many venom components
  – Variation possible based on species, geography, age

• Clinical Effects from envenomations are unpredictable
  – Evaluate for Local, Hematologic, and/or Systemic
  – Treat the patient, not the snake

• First do no harm
  – No prehospital treatment is effective
  – Antivenom is the definitive treatment
If you have treated ONE snakebite, you have treated THAT snakebite.
I feel better prepared to treat the next patient I see with Pit Viper envenomation

a. True  
b. False  
c. I’m hungry  
d. Sorry, I fell asleep
REFERENCES


Thank you...

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