Learning Objectives

Upon completion, participants should be able to:
• Recognize the effects of resulting symptoms of snake envenomation on patients’ daily functioning
• Evaluate the benefits and limitations of using crotaline Fab antivenom to treat pit viper envenomation
• Identify best practices for the assessment, treatment, and follow-up care of patients presenting with pit viper envenomation
Objectives

• North American Snake Envenomation
  – The snakes
  – The venom
  – How to assess the patient

• Antivenoms
  – What are they?
  – How do they work?
  – Efficacy and adverse effects
  – Copperhead controversy

• Management
  – Prehospital, ED/inpatient, post discharge
  – Cases

Snakes of North America

• Crotaline
  – Rattlesnakes
  – Pygmy rattlesnake
  – Cottonmouths and copperheads

• Non-crotaline
  – Coral snakes
  – Exotic snakes
  – Non-venomous snakes

North American Pit Vipers

• Rattlesnakes
  – *Crotalus*

North American Pit Vipers

• Pygmy rattlesnakes
  – *Sistrurus*
North American Pit Vipers

- Cottonmouth (*Agkistrodon piscivorus*)
- Copperhead (*A. contortrix*)

Epidemiology

- 4,000 to 9,800 patients/year\(^1-3\)
- 98% crotaline\(^2\)
- 44% copperhead\(^2\)

Pit Viper Venom

• Purpose: immobilize and digest prey
• Complex mixture
  – 90% protein
• 3 main functions:
  – Tissue digestion
  – Inflammatory/vasodilatory
  – Anticoagulant/antiplatelet


Venom Effects

• Venom effects
  – Tissue injury
  – Hematologic
  – Systemic
    ▪ Cardiovascular
    ▪ Neurologic
    ▪ Gastrointestinal
    ▪ Pulmonary
    ▪ Renal

Local Tissue Effects

- Inflammation
- Subcutaneous edema
- Skin and muscle necrosis
- Lymphatic injury

Hematologic Venom Effects

- Thrombocytopenia—platelet activation and clumping\(^1,2\)
- Defibrinogenation—cleavage of fibrinogen into effective split products\(^1,2\)
- Increased PT, PTT\(^1,2\)
- May occur in the initial phase or days later

---

Systemic Venom Effects

• Cardiovascular
  – Heart rate
  – Blood pressure
  – Cardiovascular collapse
• Pulmonary
  – Dyspnea, tachypnea, hypoxia
  – Pulmonary edema
• Gastrointestinal
  – Vomiting, pain
• Renal
• Neurologic
  – Myokymia, fasciculation
  – Apprehension, confusion, coma


Assessing Severity/Progression

• Tissue injury
  – Mark leading edge and follow over time
• Hematologic effects
  – CBC, fibrinogen, coagulation parameters
• Systemic effects
  – Vital signs, assess for neurologic signs
• No longer recommended in clinical practice
  – Circumferential measurements
  – Snakebite grading scales

Objectives

• North American Snake Envenomation
  • The snakes
  • The venom
  • How to assess the patient
• Antivenoms
  – What are they?
  – How do they work?
  – Efficacy and adverse effects
  – Copperhead controversy
• Management
  – Prehospital, ED/inpatient, post discharge
  – Cases

Antivenoms

• Antibodies produced and recovered from vertebrate animals
• First-generation antivenoms:
  – Intact IgG
  – Crude purification
  – Protein aggregates
  – Acute hypersensitivity reactions
  – Serum sickness
• Modern antivenoms:
  – Cleaved IgG (Fab or F(ab’)2)
  – Highly purified
  – Adverse reactions less common and less severe
  – Recurrence

## Pit Viper Antivenoms

<table>
<thead>
<tr>
<th></th>
<th>Antivenin (Crotalidae) Polyvalent [ACP]¹</th>
<th>FabAV Crotalidae Polyvalent Immune Fab (ovine) [CroFab]²</th>
<th>F(ab')2 AV Crotalidae Immune F(ab')2 (Equine) [Anavip]³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years available</td>
<td>1954 - 2002</td>
<td>2000 to present</td>
<td>2018 to present</td>
</tr>
<tr>
<td>Source animal</td>
<td>Horse</td>
<td>Sheep</td>
<td>Horse</td>
</tr>
<tr>
<td>Molecule</td>
<td>Serum globulins</td>
<td>Fab</td>
<td>F(ab')2</td>
</tr>
<tr>
<td>Additional purification</td>
<td>Fractionation</td>
<td>Fractionation and affinity purification</td>
<td>Fractionation</td>
</tr>
<tr>
<td>FDA approval</td>
<td></td>
<td>Rattlesnakes</td>
<td>Rattlesnakes only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cottonmouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Copperhead</td>
<td></td>
</tr>
</tbody>
</table>


## Antivenom Therapy: Indications*

- Acute local tissue symptoms
- Significant coagulopathy (thresholds arbitrary)
  - INR > 2
  - Fibrinogen < 50 mg/dL
  - Platelets < 50,000 cells/µL
  - Unfavorable trend
- Systemic venom effects
- Additional antivenom
  - Progression of envenomation syndrome despite treatment
  - Maintenance therapy may be needed to prevent recurrence of limb swelling

Fab and F(ab’)2 Antivenom: Efficacy

• Fab
  – Tissue injury
    ▪ Halts progression of limb injury\(^1\)
    ▪ Reduces recovery time\(^2\)
    ▪ Early treatment produces better outcomes\(^2\)
  – Improves coagulation derangements\(^3\)
  – Improves systemic symptoms\(^4\)

• F(ab’)2*
  – Initial control achieved by halting the symptoms of envenomation\(^5,6\)
  – Post-treatment recurrence and late-onset coagulopathy\(^5,6\)

5. Crotalidae Immune F(ab’)2 [package insert]. Rare Disease Therapeutics, Inc; Franklin, TN 2018.

* F(ab’)2 available October 2018 and evaluated for coagulation only.

Fab Antivenom Adverse Effects: Acute Hypersensitivity Reactions

• Fab
  – Occurs in 8% of patients\(^1\)
  – Usually mild
    ▪ ~1% antivenom not restarted
  – “Treat through” most mild reactions

Fab Antivenom Adverse Effects: Serum Sickness

• Fever, muscle/joint pain, rash\(^1\)
• Caused by excess foreign protein\(^1\)
  – Unknown how much due to venom vs antivenom
• Occurs in about 13% of treated patients\(^1\)
• Rarely serious with Fab antivenom


Copperhead Controversy: Copperheads vs Rattlesnakes

• Copperhead bites generally have\(^1-4\):
  – Less severe venom effects
    ▪ Significant overlap
  – Less coagulopathy and thrombocytopenia
  – Death following copperhead bite is very rare
• Primary effect is local tissue injury\(^5,6\)
  – Most patients: disability lasting 1 to 3 weeks
  – Some patients (20%) experience lasting disability

Copperhead Controversy Update

• Historic approach
  – Second-generation antivenom safety concerns
  – Old axiom “treatment worse than disease”

• New approach
  – Severity in coagulation derangements is variable\(^1\)
  – Fab antivenom safety profile
  – Demonstrated efficacy\(^2\)
  – Risk/benefit favors Fab antivenom
  – Primary issue is cost/benefit

---


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\(^1\)

• Multicenter, randomized, double-blind: 18 EDs
• Patients with mild to moderate severity copperhead envenomation
• N = 74 (45 FabAV, 29 placebo)
• 53% men
• Mean age = 43 years (range 12 to 86 years)
• 62% had lower-extremity envenomation
• 88% had mild initial severity

---

Results: Primary Efficacy Endpoint
Limb Function Recovery at 14 Days

• Patient-reported functional recovery scale of 0-10
  – Difference: 1.2; 95% CI, 0.1-2.3; \( P = .04 \)
  – Statistically significant\(^1\)
• Clinically significant\(^2,3\)
• Treatment-related adverse effects: 36% FabAV vs 10% placebo\(^1\)

---

Results: Additional Outcomes

• Routinely favored FabAV vs. placebo: DASH, LEFS, grip strength, NPRS, PROMIS PF-10\(^1\)
• Opioid analgesic use\(^2\)
  – Placebo group was 5.5 times more likely to be on opioids during recovery than the antivenom group

<table>
<thead>
<tr>
<th>Day</th>
<th>Opioid Use (FabAV) (%)</th>
<th>Opioid Use (Placebo) (%)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>34.1</td>
<td>42.9</td>
<td>8.8</td>
</tr>
<tr>
<td>7</td>
<td>27.3</td>
<td>39.3</td>
<td>12.0</td>
</tr>
<tr>
<td>10</td>
<td>11.4</td>
<td>28.6</td>
<td>17.2</td>
</tr>
<tr>
<td>14</td>
<td>4.5</td>
<td>25.0</td>
<td>20.5</td>
</tr>
<tr>
<td>17</td>
<td>4.5</td>
<td>25.0</td>
<td>20.5</td>
</tr>
<tr>
<td>21</td>
<td>0.0</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>24</td>
<td>0.0</td>
<td>10.7</td>
<td>10.7</td>
</tr>
<tr>
<td>28</td>
<td>0.0</td>
<td>7.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

\( OR = 0.18 \, (0.05, 0.64), \ P = .008 \)

---

Recovery by Time to Treatment
Fab Antivenom Group

Days Post-Envenomation

Recovery by Days Post-Envenomation, %

Early < 5.47 hours
Late 5.47 hours

$P = .025$

Presenting severity is not final severity
- Risk of progression

Safety

Efficacy
- Recovery of function
- Pain
- Quality of life

Pros/Cons of Treating Copperhead and/or Mild Envenomation

Pro

- Presenting severity is not final severity
  - Risk of progression
- Safety
- Efficacy
  - Recovery of function
  - Pain
  - Quality of life

Con

- Cost
- Most recover

New axiom “offer Fab antivenom if symptomatic”
Objectives

• North American Snake Envenomation
  – The snakes
  – The venom
  – How to assess the patient

• Antivenoms
  – What are they?
  – How do they work?
  – Efficacy and adverse effects
  – Copperhead controversy

• Management
  – Prehospital, ED/inpatient, post discharge
  – Cases

Prehospital\textsuperscript{1,2}

<table>
<thead>
<tr>
<th><strong>Do’s</strong></th>
<th><strong>Don’ts</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• ABCs</td>
<td>• Cut</td>
</tr>
<tr>
<td>• Reassure patient</td>
<td>• Suction</td>
</tr>
<tr>
<td>– Stay calm</td>
<td>• Ice</td>
</tr>
<tr>
<td>• Transport</td>
<td>• Use electricity</td>
</tr>
<tr>
<td>• Position extremity</td>
<td>• Use tourniquets</td>
</tr>
</tbody>
</table>

ED/Hospital Initial Care

**Do’s**
- ABCs
- Assess patient
- Offer reassurance
- Call expert
- Update tetanus
- Control pain
- Properly position
  - Elevate once antivenom is given
- *Antivenom algorithm*

**Don’ts**
- NSAIDs?
- Steroids
- Fasciotomy
  - Prophylactically
  - Without antivenom
  - Without compartment pressures


---

**Fab Antivenom Algorithm Goals: Obtain and Maintain Control**

**Obtain Control:**
- Dry Bite: Observe
  - No
  - Symptoms of Envenomation → Yes
  - Administer Antivenom (4-6 vials)
  - No
  - Initial Control
  - Yes

**Maintain Control:**
- Discharge Criteria Met
  - No
  - Progression (Monitor)
  - Yes
  - Additional Antivenom
  - Maintenance (2 vials: 6, 12, 18 hrs)

Fab Antivenom Algorithm Goals: Obtain and Maintain Control

1. Obtain Control:
   - Dry Bite: Observe
   - Symptoms of Envenomation
     - Yes: Administer Antivenom (4-6 vials)
     - No: Initial Control
   - Initial Control

   “Initial control”
   - Swelling no longer progressing
   - PT, fibrinogen, platelets normal or improving
   - No major systemic venom effects

2. Offer vs administer
   - Mild vs moderate/severe
   - Most progress\(^1\)
   - Time is tissue

3. Choose initial dose
   - Assess risk factors for severity
   - Example: children, hand, presenting severity, etc.

Assessing Severity/Progression

• Assessment
  – Tissue injury
    ▪ Pain, tenderness, swelling, ecchymosis, erythema
    ▪ Leading edge
    ▪ Patient gestalt “same, better, or worse?”
  – Hematologic effects
    ▪ Labs: platelets, fibrinogen, PT/PTT
    ▪ Bleeding
    ▪ Trends vs isolated values
  – Systemic effects
    ▪ Vital signs
    ▪ Signs/symptoms
    ▪ Labs

Fab Antivenom Algorithm Goals: Obtain and Maintain Control

• Do all patients require maintenance?
• Options:
  • Most mild/moderate patients receive ~10 vials\(^1\)
  • Administer as needed
  • Scheduled

Maintain Control:

Fab Antivenom Algorithm Goals: Obtain and Maintain Control

• How frequently should I reevaluate the patient?
• Differentiating progressive tissue symptoms vs redistribution of fluid due to gravity
• Absolute lab number vs trend

Maintain Control:

- Discharge Criteria Met
- Progression (Monitor)
- Maintenance (2 vials: 6, 12, 18 hrs)
- Additional Antivenom

Yes
No

Fab Antivenom Algorithm Goals: Obtain and Maintain Control

• No progression of any venom effect
• Labs trending in correct direction
• No antivenom “on board”
• Discharge instruction
  • Serum sickness
  • Follow-up labs

Maintain Control:

- Discharge Criteria Met
- Progression (Monitor)
- Maintenance (2 vials: 6, 12, 18 hrs)
- Additional Antivenom

Yes
No

Case Discussions
How would you manage these patients?

Case 1: Standard Envenomation

- 25-year-old intoxicated man
- Right foot bite with surrounding ecchymosis
- 1 hour prior to arrival
- Vitals: tachy 112, nausea
- Pain, swelling to mid-calf
- Platelets: 80k
- Fibrinogen: 150
Case 1: Resolution

Obtain Control:
- Yes: Initially Control
- No: Obtain Control

- Symptoms of Envenomation
- Administer Antivenom (4-6 vials)
- Initial Control
- No: Progression (Monitor)
- Yes: Maintenance (2 vials: 6, 12, 18 hrs)
- Additional Antivenom
- Discharge Criteria Met

Maintain Control:
- Yes: Discharge Criteria Met
- No: Progression (Monitor)

Case 2: Severe Envenomation

- 2-year-old child
- Right index finger bite
- 30 minutes prior to arrival
- Vitals:
  - HR, 165; BP, 70/P; RR, 38
- Pain, swelling to elbow
- Fingertip hemorrhagic bullae
- Platelets: 40k
- Fibrinogen: 60

Case 2: Resolution

Obtain Control:
- Symptoms of Envenomation
  - Yes: Observe
  - No: Administer Antivenom (4-6 vials)
- Initial Control
  - Yes: Discharge Criteria Met
  - No: Progression (Monitor)

Maintain Control:
- Progression (Monitor)
  - No: Maintenance (2 vials: 6, 12, 18 hrs)
  - Yes: Additional Antivenom

Case 3: Mild Envenomation

- 40-year-old female landscaper
- Copperhead bite right foot
- 1 hour prior to arrival
- Pain, edema, ecchymosis of foot
- Below ankle
- Vitals stable
- Platelets/fibrinogen normal

Case 3: Resolution

Obtain Control:

- Dry Bite: Observe
- Administer Antivenom (4-6 vials)

Initial Control

Maintain Control:

- Discharge Criteria Met
- Progression (Monitor)
- Additional Antivenom

Maintenance (2 vials: 6, 12, 18 hrs)

Conclusions

• Antivenom is current cornerstone of therapy
• Time to treatment matters, which drives decisions
• Assessment of control and progression is key to maximize outcomes

Thank you
Abbreviations

ABCs = airway, breathing, circulation
BP = blood pressure
CBC = complete blood count
CI = confidence interval
DASH = Disorders of the Arm, Shoulder, and Hand
ED = emergency department
Fab = fragment antigen binding
FabAV = Fab antivenom
HR = heart rate
IgG = Immunoglobulin G
INR = international normalized ratio
LEFS = Lower Extremity Functional Scale
NPRS = numeric pain rating scale
NSAID = nonsteroidal anti-inflammatory drug
PROMISE PF-10 = Patient-Reported Outcomes Measurement Information System Physical Function-10
PT = prothrombin time
PTT = partial thromboplastin time
RR = respiratory rate

Acknowledgment of Commercial Support

This activity is supported by an educational grant from BTG International Inc.

Contact Information

Call (toll-free) 866 858 7434
Email info@med-iq.com

Please visit us online at www.Med-IQ.com for additional activities provided by Med-IQ®.
To receive credit, click the “Get Credit” tab at the bottom of the webcast for access to the evaluation, attestation, and post-test.

© 2018

Unless otherwise indicated, photographed subjects who appear within the content of this activity or on artwork associated with this activity are models; they are not actual patients or doctors.