**TAKING THE BITE OUT OF SNAKE BITES**

**ANTI-VENOM OPTIONS**

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**OBJECTIVES**

- Review general care for snake bites
- Review new literature relating to initial control and maintenance dosing
- Discuss place in therapy for new F(ab)'2 snake antivenom

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**Eastern Diamondback Rattlesnake**

- Largest venomous snake in North America
- Can reach 8 feet in length and weigh up to 10 pounds
- Feared as deadly and aggressive
- Can strike at up to 1/3 of their body length

**TRIVIA QUESTION**

Do rattlesnakes make the rattle sound with their tail before striking/biting?

True
False

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**Venomous Snakes of Florida**

- Easily identifiable diamond pattern with beige borders and brown centers (hence the name) makes it easy to spot these snakes
FALSE

• Some people wrongly believe the Eastern Diamondback Rattlesnake must rattle before striking
• Lay silent and motionless, then strike without the usual nervous buzz from its rattle
• Rattlesnakes that rattle are more apt to be heard, seen, and killed, and those that remain silent are more apt to go undiscovered

Do

• Keep calm
• Remove rings/jewelry, constricting clothing
• Immobilize extremity if possible
• Keep bitten area at heart level or below
• Wash bitten area gently
• Sutherland Wrap
• Go to nearest ED

Do Not

• Cut open and suck
• Apply tourniquet
• Use ice
• Try to catch snake
• Give NSAIDs, prophylactic antibiotics or steroids
• Feed the victim

UPON ARRIVAL TO ER

• Mark leading edge of swelling every 15-30 minutes
• Treat pain with IV opioids is preferred therapy
• Lab values
  • Prothrombin time
  • INR
  • Hemoglobin
  • Platelets
  • Fibrinogen
• Assess allergies
• Tetanus vaccination
• Contact poison control center (800-222-1222)

“DRY BITE”

• 20-25% of crotaline snakebites are “dry”
• This means there is no venom injection
• Patients can still develop signs of envenomation after a latent period
• Management
  • Do not administer antivenom
  • Observe patient for >8 hours
  • Repeat labs prior to discharge
  • If the patient develops signs of envenomation, check for indications for administration of antivenom

INDICATIONS FOR ANTIVENOM ADMINISTRATION

• Any of the following
  • Progressive swelling
  • Elevated prothrombin time/INR
  • Decreased fibrinogen
  • Decreased platelets
  • Any systemic signs or symptoms

ASSESSMENT QUESTION 1
Which of the following should you NOT do if bit by a snake?

a. Remove rings/jewelry, constricting clothes
b. Keep bitten area at heart level or below
c. Apply tourniquet
d. Go to nearest ED
C. APPLY TOURNIQUET

**Do**
- Keep calm
- Remove rings/jewelry, constricting clothing
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CROFAB®

CROTALIDAE POLYVALENT IMMUNE FAB (OVINE)

- Sterile, purified, ovine-derived, polyclonal fab product
- Indication:
  - Management of patients with North American crotalid envenomation
  - Regardless of severity
  - Early use of CroFab® (within 6 hours of snakebite) is advised for treating pit viper envenomation

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INITIAL CONTROL

- Halting of the progression of local effects
  - Edema
  - Ecchymosis
- Clear trend toward improvement in coagulation abnormalities
  - Thrombocytopenia
  - Spontaneous bleeding
- Resolution of all systemic effects
  - Including: nausea, vomiting, dizziness, or tachycardia
  - Excludes: Excluding fasciculation or myokymia, which may be refractory to antivenom

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MAINTENANCE DOSING

- Initiated after initial control is established
- Additional 2 vial dose of CroFab® every 6 hours for up to 18 hours
  - 3 doses total

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DO SING

- 4 to 6 vials is the recommended initial dose
- Patient should be observed for up to 3 hours following the completion of the initial dose to determine if initial control of the envenomation has been achieved
- If initial control not achieved by the first dose, an additional 4 to 6 vials should be administered until initial control of the envenomation has been achieved

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ASSESSMENT QUESTION 2

What is the initial dose for CroFab®?

a. 1 gram  
b. 4-6 Vials  
c. 2 Vials  
d. 3 vials

B. 4-6 VIALS

Crotalidae polyvalent immune fab (Ovine) [CroFab®]. [Medication information. CrotFab.com]

FACTORS ASSOCIATED WITH DIFFICULTY ACHIEVING INITIAL CONTROL

- Secondary analysis of crotaline snakebites from 2002-2004 to predict which patients might have difficulty achieving initial control
- Venom effect definition

SEVERITY SCORE - MODIFIED

Initial control
- Simultaneous occurrence of:
  - No progressive local tissue effects
  - No systemic venom effects
  - Including no evident bleeding and all coagulation and platelet count clearly trending toward normal

TYPES OF BITES

RESULTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (yr)*</td>
<td>1.61 (0.99-2.64)</td>
<td>0.06</td>
</tr>
<tr>
<td>+40 or old compared to all other ages</td>
<td>0.99 (0.51-1.93)</td>
<td>0.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.19 (0.72-2.10)</td>
<td>0.47</td>
</tr>
<tr>
<td>Severity*</td>
<td>0.38 (0.12-1.19)</td>
<td>0.17</td>
</tr>
<tr>
<td>Treated at referral hospital</td>
<td>1.50 (0.59-4.05)</td>
<td>0.48</td>
</tr>
<tr>
<td>Time to treatment (hr)</td>
<td>1.30 (0.38-4.68)</td>
<td>0.67</td>
</tr>
<tr>
<td>Pre-hospital treatment</td>
<td>1.50 (0.59-4.05)</td>
<td>0.48</td>
</tr>
<tr>
<td>Survival rate of patients &amp; treatment outcome</td>
<td>0.28 (0.10-0.78)</td>
<td>0.01</td>
</tr>
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<td>1.50 (0.59-4.05)</td>
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</table>
RESULTS

- Both thrombocytopenia and neurologic effects
  - 13.8 fold increase
- Risk for difficulty achieving initial control
- Thrombocytopenia, neurologic effects, coagulopathy and severe bites were significantly associated with patient who required more than 12 vials to achieve initial control or did not achieve initial control
- Overall presence of thrombocytopenia or neurologic venom effects prior to treatment with anti-venom were significantly and independently associated with difficulty achieving initial control

Yin S, et al. ACAD EMERG MED. 18:1; 46-52

NEW THERAPY OPTION

ANAVIP®
Crotalidae Immune F(ab’)2 Equine

- Approved 2015
- Sterile, lyophilized, equine-derived, polyvalent preparation of equine immunoglobulin F(ab’)2 fragments
- Indicated for management of adult and pediatric patients with North American rattlesnake envenomation

CROTALIDAE IMMUNE F(AB’)2 EQUINE

DOSing

<table>
<thead>
<tr>
<th>Dose</th>
<th>No of Vials</th>
<th>Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>10 vials</td>
<td>Over 60 min</td>
</tr>
<tr>
<td>Additional doses to achieve initial control</td>
<td>10 vials PRN (no known max dose)</td>
<td>Over 60 min</td>
</tr>
<tr>
<td>Observation and late dosing</td>
<td>4 vials</td>
<td>Over 60 min</td>
</tr>
</tbody>
</table>

ASSESSMENT QUESTION 3

What of the following are true about Crotalidae Immune F(ab’)2 Equine?

a. Is a sterile, lyophilized, equine-derived, polyvalent preparation of equine immunoglobulin F(ab’)2 fragments
b. The initial dose is 10 vials
c. Can give an additional 2 vial dose every 6 hours for up to 18 hours
d. A and B
e. A and C

D. A AND B

- a. Is a sterile, lyophilized, equine-derived, polyvalent preparation of equine immunoglobulin F(ab’)2 fragments
- b. The initial dose is 10 vials
Phase 2, prospective, randomized, open label, controlled clinical trial

Comparing (Fab')2 with Fab antivenom treatment in the management of rattlesnake bite envenomation

Pharmacokinetic studies involving (Fab')2 antivenom are common in Latin America but not in the United States

(Fab')2 is a smaller Fab molecule and may result in longer plasma persistence of antivenom

Study medications
- Fab = Crotalidae polyvalent immune Fab (Ovine) ➔ CroFab®
- (Fab')2 = Crotalidae equine immune Fab (Fab')2 ➔ Anavip®

Outcomes

The primary clinical efficacy variable
- Quantitative serum venom level
  - Hypothesized that this would drop to less than 10% of the original level between time of presentation and initial control

Secondary endpoints
- Quantitative plasma antivenom levels
- Fibrinogen
- Platelet count
  - Hypothesized that the longer duration of action of (Fab')2 would be evident in longer plasma persistence of measurable antivenom relative to Fab


Patient selection

Efficacy endpoints

Results

Venom levels dropped below detection limits in all patients following initial treatment

Subsequently rebounded into the measurable range in 4 of 6 fab cases

(Fab')2 antivenom levels demonstrated a longer plasma persistence than fab levels

Less rapid drop during the two days following treatment

Two patients in the fab group had significant adverse events involving coagulation abnormalities
  - Additional antivenom was administered following the initial treatment period

Bush SP, et al. Clinical Toxicology. 2015. 53:137-45
OUTCOMES

- Primary efficacy endpoint
  - Coagulopathy between the end of maintenance dosing and study day 8
    - Coagulopathy defined as
      - Platelet count less than 150,000/mm³ or
      - Fibrinogen less than 150 mg/dl or
      - Use of antivenom to treat a coagulation abnormality between the end of maintenance dosing and study day 5

- Secondary efficacy endpoints
  - Platelet counts
  - Fibrinogen levels
  - Venom levels

Efficacy Endpoints

- Fab'2 antivenom can reduce subacute coagulopathies following treatment compared to using Fab antivenom
- Results implies that the use of Fab'2 antivenom could reduce medically significant late bleeding after a snakebite
- The need for repeated blood testing after treatment might be able to be reduced
- Maintenance dosing is not required with Fab'2 to prevent late coagulopathy

SUMMARY

- Crofab Dosing
  - Initial 4-6 vials, wait one hour and observe for initial control
  - Re-dose with initial dosing if control not gained
  - Maintenance dosing 2 vials every 6 hours for 3 doses
- AnaVip Dosing
  - Initial 10 vial dose and observe for initial control
  - Re-dose with initial dosing if control not gained
  - Maintenance dosing 4 vials as needed for recurrence of symptoms
  - May need at least one or more re-dosing with initial dose to gain initial control
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REFERENCES

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