Learning Objectives

1. Discuss the pathophysiology, toxicology, and clinical management of pit viper envenomations
2. Review the pharmacology of crotalidae polyvalent immune Fab antivenom (CroFab®)
3. Analyze evidence for as needed crotalidae antivenom maintenance dosing strategy compared to the FDA-approved, scheduled maintenance dosing and apply to a patient with crotaline snakebite
Assessment Questions

1. Which of the following snake venoms is NOT covered by CroFab®?
   a. Western & eastern diamondback rattlesnake
   b. Texas coral snake
   c. Mojave rattlesnake
   d. Copperhead
   e. Cottonmouth
   f. Both b and d

2. Patients with snakebite envenomation should be monitored for
   a. Local tissue swelling
   b. Coagulopathy and bleeding
   c. Hypotension
   d. Neurotoxicity
   e. All of the above

3. True/False: Crotalidae polyvalent immune Fab lacks the Fc portion of the IgG antibody, making it less immunogenic than the whole antibody.
   a. True
   b. False

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Faculty (Speaker) Disclosure: Ashley E. Lock has indicated she has no relevant financial relationships to disclose relative to the content of her presentation.
Background

I. Epidemiology
   A. There are more than 3,000 species of snakes worldwide, including ~800 species of venomous snakes\(^1\)
      1. Around 30 venomous species live in United States (US)\(^1\)
      2. Most active in warmer months, April through November\(^1,2\)
   B. About 5,000 reported snakebites in the US annually\(^1\)
      1. According to North American Snakebite Registry, 99% of snakebites are from pit vipers\(^3\)
   C. Males disproportionately affected by snakebites (69.3% of cases)\(^3\)
   D. Lower extremity snakebites account for 54% of envenomations\(^3\)
   E. Mortality is low (<10 fatalities annually or 0.5%)\(^1,4\)
      1. Prior to antivenom in the 19\(^{th}\) century, mortality from pit vipers ~5-25%\(^4\)
   F. Morbidity can be significant depending on variables, such as:
      1. Snake species
      2. Envenomation severity
      3. Bite location (i.e. face/neck vs. extremities)
      4. Venom deposition (i.e. intravascular vs. intramuscular/subcutaneous)
      5. Patient comorbidities

II. Etiology
   A. Families of venomous snakes\(^1\)
      1. Elapidae
         a. Characteristics: fixed front fangs, smooth scales, neurotoxic venom
         b. Examples: cobra, coral snake, death adder, black mamba
      2. Viperidae
         a. Characteristics: retractable front fangs, rough scales, triangular head, hematologic or neurotoxic venom
b. Viperidae includes the subfamilies, Crotalinae and Sistrurus, known as “pit vipers”
c. Examples: western and eastern diamondback rattlesnake, Mojave rattlesnake, cottonmouth, copperhead

III. Venom toxicology
   A. Toxicokinetic data limited to non-US snake case reports and animal data
   B. Venom protein size range: 6-100 kilodaltons
   C. Variability in venom protein absorption
   D. Large volume of distribution to tissues via lymphatic system
   E. Elimination half-life: 5 – 39 hours
   F. Venom blood concentrations correspond with severity of coagulopathy

IV. Envenomation pathophysiology
   A. Local effects
      1. Metalloproteases, hyaluronidase, and phospholipase A₂
         a. Structural damage
            i. Extracellular matrix (e.g. collagen, hyaluronan)
            ii. Basement membrane of blood vessels
      2. L-amino acid oxidases
         a. Produce ammonia and hydrogen peroxide, inducing cell apoptosis
      3. Increased permeability of damaged endothelium to fluid and inflammatory mediators leads to local edema and tissue necrosis
   B. Circulatory effects
      1. Kallikrein-like serine protease
      2. Natriuretic peptides
         a. Increase cyclic guanosine monophosphate (cGMP) levels
         b. Inhibit angiotensin converting enzyme (ACE)
      3. Large fluid shift through damaged endothelium into tissues leads to distributive shock
      4. RAAS antagonism leads to vasodilation and hypotension
   C. Hematologic effects
      1. Venom contains procoagulant, anticoagulant, and antiplatelet proteins
      2. Phospholipase A₂
         a. Phospholipid membrane hydrolysis and red blood cell hemolysis
      3. Procoagulant proteins

RAAS = renin-angiotensin-aldosterone system

Figure 5: Venom Proteins and Toxicologic Effects

Local
- Metalloprotease
- Hyaluronidase
- Phospholipase A₂
- L-amino acid oxidase

Circulatory
- Kallikrein-like serine protease
- Natriuretic peptides
- RAAS antagonism

Hematologic
- Procoagulants
- Anticoagulants
- Disintegrins
- C-type lectin like proteins

Neuromuscular
- Phospholipase A₂
- Acetylcholine inhibition
- Myotoxin A
- Crotamine

LOCK | 4
a. Prothrombin activators  
b. Factor X and V activators

4. Anticoagulant proteins  
a. Thrombin-like enzymes (i.e. fibrinogenases)

5. Platelets  
a. Disintegrins prevent platelet aggregation  
b. C-type lectin like proteins promote or prevent platelet aggregation  
c. Increased platelet consumption via aggregation and sequestration in damaged tissue

D. Neuromuscular effects

1. Acetylcholinesterase  
a. Acetylcholine breakdown prevents neurotransmission  
b. Results in flaccid paralysis

2. Myotoxin A, crotamine, and phospholipase A₂  
a. Toxic to myocyte calcium channels and sarcoplasmic reticulum  
b. Results in tetanic paralysis

**Pit Vipers**

I. Types of pit vipers

<table>
<thead>
<tr>
<th>Table 1. Texas Pit Vipers²</th>
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<tbody>
<tr>
<td><strong>Genus</strong></td>
</tr>
<tr>
<td><strong>Species</strong></td>
</tr>
<tr>
<td>Diamondback Mojave Timber Mottled Rock Banded Rock Blacktail Prairie</td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
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<tr>
<td><strong>Habitat</strong></td>
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<tr>
<td><strong>Region</strong></td>
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</tbody>
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TX = Texas
II. Pit viper venom
   A. 20-25% are dry bites\(^\text{10}\)
   B. Among wet bites, 0.1 – 1 g venom can be injected per bite\(^\text{1}\)
   C. Pit vipers inject 75% more venom than other snake families\(^\text{5}\)
   D. Venom composed of 50-100 enzymatic and toxin proteins
      1. Highly stable proteins resistant to temperature changes and desiccation\(^\text{4}\)
      2. Predominant proteins: phospholipase A\(_2\), metalloproteases, serine proteases\(^\text{5}\)

Clinical Presentation
I. Significant severity variability: snake species, venom composition, location of bite, patient response, symptom onset\(^\text{11}\)
   A. 90% of patients will have local tissue damage and pain
   B. Local symptoms develop within 30-60 minutes\(^\text{4}\)
   C. Hematologic recurrence occurs in 20-50% of patients\(^\text{9}\)
II. Local effects
   A. Pain, tissue necrosis, progressive inflammation, edema, decreased mobility
   B. Compartment syndrome (CS)
      1. Potentially limb-threatening condition
      2. Increased muscle swelling compresses blood vessels and nerves
      3. Swelling and paresthesias secondary to envenomation may progress to CS
      4. Management\(^\text{4}\)
         a. Elevate affected limb and load with 4-6 vials CroFab\(^\text{®}\) if not administered within the previous hour\(^\text{4}\)
         b. Consider fasciotomy: refractory compartment pressure (≥30 mmHg), circulatory insufficiency ≥4 hours after antivenom\(^\text{4}\)
         c. Fasciotomy risks: increased length of stay, nerve/tissue damage, decreased functional limb mobility\(^\text{12}\)
III. Systemic effects\(^\text{4}\)
   A. Nausea/vomiting (N/V), lethargy, myokymia, perioral paresthesia with mint or metallic taste, tingling of distal extremities
   B. Hypotension, vasodilation, tachycardia, dyspnea, altered mental status, angioedema, anaphylactoid reaction
IV. Hematologic effects\(^\text{4,10}\)
   A. Bleeding gums, epistaxis, ecchymosis, oozing at bite site, hematuria, hemoptysis, gastrointestinal bleed, intracranial hemorrhage
   B. Ecchymosis presents 3-6 hours after rattlesnake bites
   C. Late coagulopathy occurs in ~1.1% of pit viper envenomations\(^\text{3}\)
V. Venom-induced consumption coagulopathy (VICC)\(^\text{8}\)
   A. Pathophysiology: coagulation cascade activation by procoagulant proteins targeting various clotting factors
   B. Around 33-50% of VICC cases recur after CroFab\(^\text{®}\) treatment\(^\text{13}\)
   C. Abnormal labs: elevated PT/INR, low or undetectable fibrinogen, D-dimer ten times the upper limit of normal, thrombocytopenia
   D. Early coagulopathy is a predictor of late coagulopathy\(^\text{14}\)
      1. Hypofibrinogenemia, positive D-dimer, thrombocytopenia, 20% increase in platelets ≤4 hour post-CroFab\(^\text{®}\)\(^\text{15}\)
2. Absence of early coagulopathy does not preclude possibility of late coagulopathy  
E. Early thrombocytopenia: caused by platelet-aggregating venom components, reversible with antivenom  
F. Late thrombocytopenia: peripheral sequestration of platelets at envenomation site, less responsive to antivenom  

VI. Proposed mechanisms for late coagulopathy recurrence  
A. Venom-antivenom mismatch  
   1. Free CroFab® is cleared faster than some venom proteins  
B. Venom-antivenom complex dissociation in circulation  
C. Depot of venom at envenomation site

Pharmacologic Treatment  
I. Indications for antivenom  
   A. Local tissue injury progression  
   B. Hematologic abnormalities  
   C. Systemic effects  
   D. Neurotoxicity  

II. Antivenom history  
   A. Antivenin (Crotalidae) Polyvalent (ACP) (equine)  
      1. First antivenom in United States (1954)  
      2. Removed from market  
      3. Elimination half-life: 15 days  
      4. Associated with high rate of hypersensitivity reactions (20-25% of patients), including some deaths from anaphylaxis  
         a. Whole IgG antibody highly immunogenic due to Fc portion  
         b. Serum sickness: 50-75% of patients  
         c. Risks of ACP antivenom outweighed benefits to many providers

<table>
<thead>
<tr>
<th>Envenomation Severity</th>
<th>Number of Vials IV</th>
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<tbody>
<tr>
<td>Minimal</td>
<td>2-4</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-9</td>
</tr>
<tr>
<td>Severe</td>
<td>≥10-15*</td>
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</tbody>
</table>

IV. CroFab® pharmacology  
   A. Mechanism of action: binds and neutralizes venom components, aiding in redistribution away from target tissues and elimination from the body

III. Crotalidae polyvalent immune fab (ovine) (CroFab®)  
   A. FDA-approved in 2000  
   B. Venom-specific Fab fragment of immunoglobulin G (IgG)  
   C. CroFab® is 5 times more potent than ACP

IV. CroFab® pharmacology  
   A. Mechanism of action: binds and neutralizes venom components, aiding in redistribution away from target tissues and elimination from the body
V. Pharmacoeconomics
   A. Average wholesale price per vial is ~$3,800\textsuperscript{22}
      1. Package insert dosing strategy utilizes a minimum of 10 vials \textsuperscript{3}

VI. CroFab\textsuperscript{®} pharmacokinetics
   A. Absorption: IV administration confers 100\% absorption\textsuperscript{20}
   B. Distribution half-life: 2.5 hours\textsuperscript{16}
      1. Compared to whole IgG antibodies, Fab fragments display more rapid
         distribution into tissues and renal clearance\textsuperscript{23}
   C. Elimination half-life: 12 – 30 hours\textsuperscript{19}
   A. Excretion: renal

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**Figure 6. CroFab\textsuperscript{®} Fab Fragment**

**Figure 7. CroFab\textsuperscript{®} Production Process\textsuperscript{19,20}**

Sheep IgG antibodies digested by papain (proteolytic enzyme in papayas), separating Fab
fragments from immunogenic Fc portion\textsuperscript{20,21}
VII. Acute hypersensitivity$^{23,24}$
   A. Two types$^{23}$
      1. Anaphylactic: IgE-mediated, previously sensitized patients
      2. Anaphylactoid: complement activation, sensitized or non-sensitized patients, related to infusion rate and concentration
         a. Anaphylactoid reaction incidence: 0.6-6%$^{10,20}$
   B. Hypersensitivity incidence
      1. Acute reaction ACP vs. CroFab®: 23-56% vs. 5.4%$^{4,24}$
   C. Treatment: epinephrine, steroids, and antihistamines$^{23}$

VIII. Serum sickness
   A. Type III hypersensitivity reaction
      1. Host antibodies form immune complexes with antivenom proteins
      2. Complexes accumulate on basement membranes of skin, joints, and renal glomeruli$^{23}$
   B. Occurs 1-3 weeks after antivenom, lasts about 1 week
   C. Signs and symptoms: fever, arthralgia, rash, lymphadenopathy
   D. Treatment: analgesics, antihistamines, and steroids over 5-7 days$^4$
   E. Rate of serum sickness with ACP vs. CroFab®: 18-86% vs. 16%$^4$

IX. Dosing$^{20}$
   A. Initial dose: 4-6 vials to achieve initial control +/- additional 4-6 vials if not achieved within 1 hour
      1. For life-threatening shock or active bleed: initial dose 8-12 vials$^{10}$
   B. Maintenance dosing: 2 vials every 6 hours for 3 doses$^{20}$
   C. PRN dosing: CroFab® administration in 2-vial increments in response to envenomation progression (i.e. local, systemic, hematologic effects)$^{19}$
   D. Initial control: assess within 1 hour of first dose completion$^{20}$
      1. Cessation of local injury progression
      2. Systemic symptoms resolved
      3. Coagulation markers normalized or improving

https://www.crofab.com/CroFab/media/CroFab/Site%20Review/Chart4.svg

Figure 8. CroFab® Initial and Maintenance Dosing$^{20}$
X. CroFab® therapeutic monitoring
   A. Local effects: least reversible component\textsuperscript{19}
      1. Least reversible venom component by CroFab\textsuperscript{®} compared to cardiovascular, gastrointestinal, hematologic, and central nervous system symptoms\textsuperscript{19}
      2. Monitor hourly for local progression recurrence after initial control
   B. Systemic effects
      1. Monitor for improvement in hemodynamic stability, mental status, neuromuscular symptoms\textsuperscript{4}
   C. Hematologic effects
      1. Clotting function recovery occurs 24-48 hours after CroFab\textsuperscript{®} administration\textsuperscript{8}
      2. Increase in platelets and fibrinogen after CroFab\textsuperscript{®} administration\textsuperscript{7}
      3. Monitor for late coagulopathy 2-3 days and 5-7 days after CroFab\textsuperscript{®}\textsuperscript{10}

**Management of Envenomation**

I. Snakebite management\textsuperscript{4,10,16}
   A. Treatment goals\textsuperscript{1}
      1. Determine envenomation occurrence
      2. Prevent envenomation symptom progression
      3. Limit tissue loss or functional mobility
   B. Management overview
      1. Unified Treatment Algorithm recommendations by 9 snakebite experts\textsuperscript{10}
         a. Maintenance dosing may not be needed for
            i. Minor envenomation
            ii. Institutions with close monitoring by physician expert

\begin{tikzpicture}[node distance=2cm, decisional/.style={diamond,anchor=west,draw,align=center,aspect=2,minimum width=5em}, procedural/.style={rectangle,draw,align=center,minimum width=10em}, data/.style={draw,align=center,minimum width=4em}]%}
\begin{figure}
\centering
\begin{tikzpicture}
\node [procedural] (check) {Assess Patient};
\node [decisional, below of=check] (check-en) {Check for Envenomation};
\node [procedural, right of=check-en, xshift=3cm] (check-prog) {Check for Progression};
\node [procedural, above of=check-en, yshift=-1cm] (admin) {Administer CroFab®};
\node [decisional, below of=admin, yshift=1cm] (initial-control) {Is Initial Control Achieved?};
\node [data, right of=admin, xshift=3cm] (check-dry) {Apparent Dry Bite/No Bite};
\node [data, below of=check-dry] (repeat) {Repeat CroFab®};
\node [data, right of=check-prog, xshift=3cm] (check-minor) {Apparent Minor Envenomation};
\node [data, below of=check-minor] (monitor) {Monitor Patient};
\node [data, below of=initial-control, yshift=-1cm] (discharge) {Discharge Criteria};

\draw [->] (check) -- (check-en) node [midway, above] {NONE};
\draw [->] (check-en) -- (check-prog) node [midway, above] {PRESENT};
\draw [->] (check-prog) -- (admin) node [midway, above] {NONE};
\draw [->] (admin) -- (initial-control) node [midway, above] {PRESENT};
\draw [->] (initial-control) -- (monitor) node [midway, above] {YES};
\draw [->] (initial-control) -- (repeat) node [midway, above] {NO};
\draw [->] (check-dry) -- (admin) node [midway, above] {NONE};
\draw [->] (check-minor) -- (repeat);\\
\end{tikzpicture}
\caption{Unified Treatment Algorithm of North American Pit Viper Envenomation\textsuperscript{10,21}}
\end{figure}
2. Weant K, et al. 2012: first CroFab® protocol published (Figure 10)\textsuperscript{25}
   a. Protocol did not require maintenance dosing in patients without progression after initial control (Appendix B)
   b. Clinical pharmacists involved in protocol implementation

| Intervention | • Patients (N = 75) with crotaline snakebite pre- and post-SSS protocol implementation  
|              | • Protocol developed by EM physicians and clinical pharmacists |
| Results      | • Single-center, retrospective review conducted June 2003 – 2009  
|              | • Total CroFab® vials used: PRE 4.7 vs. POST 2.5 vials (p = 0.007)  
|              | • Hospital LOS: 2.79 vs. 1.93 (p = 0.030)  
|              | • No difference: progression to fasciotomy, allergic reaction |
| Conclusion   | • Clinical protocol ↓ number CroFab® vials used and hospital LOS with no ↑ adverse effects  
|              | • Cost-savings: $2,000 per patient |

$SSS = $snakebite severity score, $EM = emergency medicine, $LOS = length of stay, $PRE = pre-SSS protocol, $POST = post-SSS protocol

Figure 10. Unified Treatment Algorithm Protocol for Clinical Use: Weant K, et al. 2012\textsuperscript{25}

<table>
<thead>
<tr>
<th>Table 3. Initial Management\textsuperscript{a}</th>
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<tbody>
<tr>
<td>Patient Assessment</td>
</tr>
<tr>
<td>Envenomation time</td>
</tr>
<tr>
<td>Snake description</td>
</tr>
<tr>
<td>Prehospital first aid interventions</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Allergies to food, drugs, &amp; sheep products</td>
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<tr>
<td>Home medications (blood thinners)</td>
</tr>
<tr>
<td>Previous envenomation history</td>
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</tbody>
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\textsuperscript{a}$PT/INR = prothrombin time, $aPTT = activated partial thromboplastin time

C. Critical lab values\textsuperscript{16}
   1. INR >3.0
   2. aPTT >50 seconds
   3. Fibrinogen <75 mg/dL
   4. Platelets <50,000 cells/mm\textsuperscript{3}
   5. No evidence to support redosing CroFab® based on critical coagulation values in the absence of clinically significant bleeding

D. Demarcate swelling above and below bite site at baseline and every 15-20 minutes until local progression stops\textsuperscript{5,9}

E. Administer bolus IV crystalloids to patients requiring antivenom and fluid resuscitation\textsuperscript{10}

F. Observe patient for ≥8-24 hours, depending on severity, for delayed S/S\textsuperscript{4}

G. Initial control is achieved in 1 hour in 50-90% of patients\textsuperscript{9}
H. Follow-up 2–3 days and 5–7 days after discharge to monitor for late coagulopathy\textsuperscript{10}

II. Antibiotics\textsuperscript{10}
- A. Wound infections rare (3% of snakebites)
- B. Prophylaxis typically unnecessary, not recommended\textsuperscript{4,10}

III. Blood products
- A. Correct VICC with CroFab\textregistered before giving blood products\textsuperscript{4}
- B. Replacing coagulation factors and platelets before adequate antivenom provides substrate for unbound venom to worsen consumptive coagulopathy\textsuperscript{8}

<table>
<thead>
<tr>
<th>Table 4. Nonpharmacologic Management</th>
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<tbody>
<tr>
<td>First Aid\textsuperscript{4,6}</td>
</tr>
<tr>
<td>- Move patient from striking distance</td>
</tr>
<tr>
<td>- Immobilize affected limb – position below heart level</td>
</tr>
<tr>
<td>- Remove constrictive clothing or accessories</td>
</tr>
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IV. Diagnosis of initial severity and progression of envenomation
- A. Gold standard: clinical assessment\textsuperscript{10}
- B. Initial severity classification
  1. No standardized definition of minimal, moderate, or severe

<table>
<thead>
<tr>
<th>Table 5. Initial Severity Assessment\textsuperscript{19,25}</th>
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<tbody>
<tr>
<td>Effects</td>
</tr>
<tr>
<td>Local</td>
</tr>
<tr>
<td>Systemic</td>
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<tr>
<td>Hematologic</td>
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S/S = signs and symptoms, N/V = nausea/vomiting, SBP = systolic blood pressure, AMS = altered mental status, INR = international normalized ratio, aPTT = activated partial thromboplastin time, plt = platelets

C. Snakebite severity score (SSS) (Appendix A) for envenomation progression\textsuperscript{11}
  1. Prior to SSS, two scoring systems used to determine envenomation severity
     a. Subjective tools
     b. Variability in snakebite severity categorization among providers

![Figure 11. Snakebite Severity Score Components\textsuperscript{11}]

CV = cardiovascular, GI = gastrointestinal, CNS = central nervous system
2. In 1996, SSS developed to objectively assess crotaline envenomation severity
   a. Retrospective study (N = 108) of reported snakebites to Western Envenomation Database\textsuperscript{11}
   b. Two physician experts evaluated patient charts and assessed severity using SSS at time of patient presentation, time of worst condition, and change in patient condition
   c. All correlations highly statistically significant
   d. All SSS components correlated highly with total SSS
3. Validation and limitations\textsuperscript{11,26}
   a. Developed as research tool to detect envenomation progression in a single patient after antivenom initiation
   b. Does not diagnose envenomation occurrence
   c. No threshold score exists at which to initiate antivenom therapy
   d. SSS cannot be used to compare patients
   e. Cannot distinguish progression from antivenom hypersensitivity

D. Snakebite Severity Score protocol for clinical use\textsuperscript{26}

<table>
<thead>
<tr>
<th>Intervention</th>
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<tbody>
<tr>
<td>Single-center, retrospective review conducted January 2010 - November 2014, in San Antonio, TX</td>
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<tr>
<td>Patients (N = 146) with crotaline snakebite pre- and post-SSS protocol implementation</td>
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<thead>
<tr>
<th>Results</th>
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<tbody>
<tr>
<td>Similar baseline characteristics</td>
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<tr>
<td>Primary outcome: total CroFab® vials used: PRE 16 vs. POST 12 vials (p = 0.006)</td>
</tr>
<tr>
<td>Secondary outcome: cost CroFab® therapy: PRE $34,000 vs. POST $26,400 (p = 0.006)</td>
</tr>
<tr>
<td>No difference: LOS, opioid use, blood product use, allergic reaction, surgical procedures</td>
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<thead>
<tr>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Snakebite protocol utilizing SSS facilitates more efficient CroFab® use with no increase in adverse outcomes</td>
</tr>
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</table>

TX = Texas, SSS = snakebite severity score, PRE = pre-SSS protocol, POST = post-SSS protocol, LOS = length of stay

Figure 12. Fowler AL, et al. Snakebite Severity Score for Clinical Use\textsuperscript{26}

Clinical Question
Is CroFab® PRN dosing as safe and efficacious as FDA-approved, scheduled maintenance dosing in patients with crotaline snakebite?

<table>
<thead>
<tr>
<th>Objective</th>
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<tbody>
<tr>
<td>Compare efficacy and safety of scheduled versus as-needed (PRN) dosing regimens of crotaline polyvalent immune Fab</td>
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<thead>
<tr>
<th>Methods</th>
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<tbody>
<tr>
<td>• Open-label, prospective, multi-center, RCT of patients with crotaline snake envenomation from June 1994 – November 1996</td>
</tr>
<tr>
<td>• First randomized trial of antivenom use in the US</td>
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<thead>
<tr>
<th>Patient Population</th>
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<tbody>
<tr>
<td><strong>Inclusion:</strong></td>
</tr>
<tr>
<td>o Minimal or moderate crotaline envenomation within 6 hours of antivenom</td>
</tr>
<tr>
<td>o Age 10 years and older</td>
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<tr>
<td>o Progression of envenomation syndrome (i.e. worsening of local tissue damage, coagulopathy, systemic symptoms)</td>
</tr>
<tr>
<td><strong>Exclusion:</strong></td>
</tr>
<tr>
<td>o Severe envenomation (i.e. airway involvement or &gt;1 limb, hemodynamic instability, life-threatening bleeding)</td>
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<tr>
<td>o Envenomation without progression</td>
</tr>
<tr>
<td>o Copperhead envenomation</td>
</tr>
<tr>
<td>o Received &gt;1 ACP vial before enrollment</td>
</tr>
<tr>
<td>o Corticosteroid use in previous 4 weeks</td>
</tr>
<tr>
<td>o Pregnancy</td>
</tr>
<tr>
<td>o Comorbidity interfering with patient exam</td>
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<table>
<thead>
<tr>
<th>Intervention</th>
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<tbody>
<tr>
<td>• <strong>Phase 1:</strong> both groups given 6 vials, with an additional 6 vials if needed, to achieve initial control</td>
</tr>
<tr>
<td>o Patients not achieving initial control with 12 vials within 6 hours were excluded</td>
</tr>
<tr>
<td>• <strong>Phase 2:</strong> maintenance vs. PRN dosing</td>
</tr>
<tr>
<td>o Maintenance: 2 vials every 6 hours for 3 doses</td>
</tr>
<tr>
<td>o PRN: 2 vials if progression of envenomation</td>
</tr>
<tr>
<td>• SSS assessed at 1, 6, and 12 hours</td>
</tr>
<tr>
<td>• Swelling measured every 2 hours from hour 6-12, and every 12 hours until hour 36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy:</strong></td>
</tr>
<tr>
<td>• No change or reduction in SSS within 12 hours after initial control</td>
</tr>
<tr>
<td><strong>Safety:</strong></td>
</tr>
<tr>
<td>• Monitoring for acute hypersensitivity while inpatient and delayed reactions after discharge (at 2, 4, 7, and 14 days)</td>
</tr>
<tr>
<td>• Recurrence: return of local or hematologic abnormality after previous resolution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severity scores compared over time using Friedman test for each patient</td>
</tr>
<tr>
<td>• Severity scores of both groups compared using 2-sided Mann-Whitney test</td>
</tr>
<tr>
<td>• Number of vials used in each group compared using 2-tailed unpaired t test</td>
</tr>
<tr>
<td>• Descriptive statistics for safety outcomes</td>
</tr>
<tr>
<td>• Fisher exact test for patients developing progression of swelling or coagulopathy recurrence</td>
</tr>
<tr>
<td>• Sample size of 28 patients needed to achieve 80% power for a 1.0 point difference in SSS</td>
</tr>
</tbody>
</table>
Results

- Baseline characteristics similar (i.e., age, race, weight, sex, bite location, initial severity)
- Median 6 vials for Phase 1 initial control
- Mean (± SD) number of vials administered PRN vs. scheduled group: 11.0 ± 4.5 vs. 13.0 ± 3.9
- Overall decrease in mean SSS: 4.35 to 2.39, p < 0.001
  - No difference between groups
- Hospital LOS <36 hours for all patients

<table>
<thead>
<tr>
<th>Recurrences per patient</th>
<th>PRN Group (n = 16)</th>
<th>Scheduled Group (n = 15)</th>
<th>Total (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (12.5%)</td>
<td>0</td>
<td>2 (6.5%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (25.0%)</td>
<td>0</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>3</td>
<td>2 (12.5%)</td>
<td>0</td>
<td>2 (6.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (50.0%)*</td>
<td>0</td>
<td>8 (25.8%)</td>
</tr>
</tbody>
</table>

*p = 0.002 compared to scheduled group

- Acute AE: 6 cases (3 cases per group); 4 mild urticaria, 2 moderate allergic reactions in patients with history of reactive airway disease
- Delayed AE: 6 patients developed serum sickness (5/6 received an unpurified lot of antivenom)

Author’s Conclusions

- Scheduled and PRN dosing regimens were equally efficacious with no clinically significant bleeding
- Additional CroFab® doses may be needed after attaining initial control
- Authors did not recommend one dosing strategy over another

Reviewer’s Critique

Strengths:
- Multi-center, RCT – important with snake species variability around US
- Used a validated severity scoring tool
- Only included patients with progressing S/S – to limit inclusion of dry bites

Limitations:
- Small sample size
- Open-label design, risk of selection bias
- Type of snake not reported – cannot account for variability in venom toxicities
- Incidence of late coagulopathy not reported

Reviewer’s Conclusion

- Fewer vials used in PRN group with similar efficacy
- Local recurrence easily managed with PRN dosing with no hematologic recurrence in hospital
- No clinically significant differences in hematologic recurrence or hypersensitivity reactions
- Conclusions cannot be drawn on PRN dosing and risk of serum sickness based on this study
- PRN dosing strategy cannot be extrapolated to patients with severe snakebite envenomation

PRN = as needed, RCT = randomized controlled trial, US = United States, SSS = snakebite severity score, SD = standard deviation, LOS = length of stay, AE = adverse effects, S/S = signs and symptoms, ACP = antivenin (Crotalidae) polyvalent

<table>
<thead>
<tr>
<th>Objective</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Characterize differences between a PRN and standard maintenance dosing (MD) strategy in hospital LOS and total antivenom usage</td>
<td></td>
</tr>
<tr>
<td>• Hypothesis: no difference in hospital LOS or number of antivenom vials used between groups</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single-center, retrospective cohort study conducted at a 658-bed hospital in Phoenix, AZ</td>
<td></td>
</tr>
<tr>
<td>• Included an established regional toxicology center responsible for envenomation management</td>
<td></td>
</tr>
<tr>
<td>• In 2011, practice policy changed from MD to PRN dosing strategy</td>
<td></td>
</tr>
<tr>
<td>• Chart review of historical controls (MD) 2007-2010 and intervention group (PRN) 2011-2014</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion:</strong></td>
<td><strong>Exclusion:</strong></td>
</tr>
<tr>
<td>• Patients ≥14 years</td>
<td>• No antivenom administered (i.e. dry bites)</td>
</tr>
<tr>
<td>• Rattlesnake envenomation</td>
<td>• Received antivenom other than CroFab®</td>
</tr>
<tr>
<td>• Admitted to regional toxicology service 2007-2014</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• PRN dosing versus MD strategy of CroFab®</td>
<td></td>
</tr>
<tr>
<td>• MD: 2 vials every 6 hours for 3 doses after initial bolus</td>
<td></td>
</tr>
<tr>
<td>• PRN: absence of MD, clinical- and laboratory-triggered dosing after initial bolus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes:</strong></td>
<td><strong>Secondary outcomes:</strong></td>
</tr>
<tr>
<td>• Hospital LOS</td>
<td>• In-hospital hemotoxicity (platelets &lt;120/mm³ or fibrinogen &lt;170 mg/dL)</td>
</tr>
<tr>
<td>• ICU LOS</td>
<td>• 60 days: readmission, retreatment, bleeding, surgery</td>
</tr>
<tr>
<td>• Total antivenom vials used</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuous variables: descriptive statistics (median and IQR)</td>
<td></td>
</tr>
<tr>
<td>• Categorical data: chi square analysis</td>
<td></td>
</tr>
<tr>
<td>• Continuous data: independent t-test and Mann-Whitney U test</td>
<td></td>
</tr>
<tr>
<td>• Power calculations performed <em>a priori:</em></td>
<td></td>
</tr>
<tr>
<td>• Required 32 patients/group to detect 50% increase in ICU or hospital LOS with 80% power and alpha 0.05</td>
<td></td>
</tr>
<tr>
<td>• Required 126 patients/group to detect 10% increase in number of vials given with 80% power and alpha 0.05</td>
<td></td>
</tr>
</tbody>
</table>
Results

- N = 310, mean age 46 years, 77% male patients, 60% upper extremity bites
- 27 cross-over cases received dosing strategy inconsistent with respective practice policy
  - Separate analysis excluding cross-overs showed no difference in outcomes
- Baseline characteristics
  - Similar on baseline characteristics (i.e. age, sex, location of bite, presence of systemic symptoms, vomiting, diarrhea, prior envenomation history)

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Maintenance (n=148)</th>
<th>PRN (n=162)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital length of stay</td>
<td>34 hr (IQR 24-43)</td>
<td>27 hr (IQR 20-44)</td>
<td>0.014</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>25 hr (IQR 20-37)</td>
<td>20 hr (IQR 16-29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total antivenom used</td>
<td>16 vials (IQR 12-18)</td>
<td>8 vials (IQR 6-12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes at 60 days*</th>
<th>Maintenance (% Total)</th>
<th>PRN (% Total)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission</td>
<td>12 (9.1)</td>
<td>12 (7.7)</td>
<td>0.831</td>
</tr>
<tr>
<td>Retreatment</td>
<td>7 (5.3)</td>
<td>6 (3.9)</td>
<td>0.583</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3 (2.3)</td>
<td>1 (0.6)</td>
<td>0.337</td>
</tr>
<tr>
<td>Surgery</td>
<td>5 (3.8)</td>
<td>4 (2.6)</td>
<td>0.737</td>
</tr>
</tbody>
</table>

*Follow-up data available for 92.6% patients overall (95.7% PRN vs. 89.2% MD)

Author’s Conclusions

- CroFab® PRN dosing strategy results in shorter hospital and ICU LOS and less total antivenom used in patients with rattlesnake envenomations versus standard MD
- Cost savings: ~$18,400 per patient

Reviewer’s Critique

**Strengths:**
- Pragmatic, objective outcomes
- Providers consistent throughout 8-year study
- Accounted for cross-over cases
- Sufficient F/U time and low loss-to-F/U rate
- Met 80% power for primary outcomes

**Limitations:**
- Single-center, retrospective study design
- 24/7 medical toxicology service not generalizable to most other institutions
- Initial severity and envenomation progression not reported

Reviewer’s Conclusion

- In the absence of a standardized clinical protocol, expert provider clinical judgment using CroFab® PRN dosing strategy significantly reduces resource utilization with no difference between PRN and MD strategies in adverse outcomes at 60 days
- Cannot extrapolate results to non-rattlesnake envenomations or pediatric patients <14 years

<table>
<thead>
<tr>
<th>Table 8. Summary of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Dart, et al. 2001</td>
</tr>
<tr>
<td>Spyres, et al. 2018</td>
</tr>
</tbody>
</table>

LOS = length of stay, ICU = intensive care unit

PRN = as needed, MD = maintenance dosing, LOS = length of stay, ICU = intensive care unit, IQR = interquartile range, AZ = Arizona, hr = hour, F/U = follow-up
Conclusion and Recommendations

I. CroFab® PRN dosing outcomes
   A. Decreased hospital length of stay and number of vials used after initial control
      1. May still need CroFab® in 2-vial increments, but less than maintenance dosing
   B. Increased cost-savings to patients and healthcare system
   C. No difference in bleeding events or need for retreatment versus maintenance dosing

II. CroFab® PRN dosing strategy should be considered
   A. For in-hospital, acute management of crotaline envenomation
   B. In patients with minimal or moderate envenomation, not severe
   C. In conjunction with
      1. A standardized management protocol incorporating SSS to assess progression
      2. Clinical judgment of healthcare providers (i.e. physicians and pharmacists)

III. Future directions: a new antivenom

   A. F(ab’)2 antivenom (F(ab’),AV) (Anavip®):
      1. FDA-approved May 2015, available on the market October 2018
      2. Two Fab fragments in a “V-shape,” produced using pepsin enzyme
      3. Derived from 2 snake venoms: Bothrops asper, Crotalus durissus
   B. Dosing: 10 vials IV plus additional 10 vials as needed for initial control, 4 vials as needed for maintenance therapy
   C. Average wholesale price per vial ~$1,500
   D. Elimination half-life: 133 hours after 1 vial
   E. Prospective, double-blind, multicenter RCT (2015): F(ab’)2 versus CroFab® and late coagulopathy occurrence after pit viper envenomation
   F. Conclusion: F(ab’),AV associated with less coagulopathy and bleeding versus CroFab®
      1. Absolute risk reduction: 19.5-24.5%
      2. Number needed to treat: 4-5 patients

References


28. Anavip(R) [package insert]. Franklin, TN: Rare Disease Therapeutics Inc; 2015.

Appendices

Appendix A. Snakebite Severity Score

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary symptoms:</td>
<td>0</td>
</tr>
<tr>
<td>• No signs/symptoms</td>
<td>1</td>
</tr>
<tr>
<td>• Dyspnea, minimal chest tightness, mild vague discomfort, respirations of 20-25 bpm</td>
<td>2</td>
</tr>
<tr>
<td>• Moderate respiratory distress, 26-40 bpm</td>
<td>3</td>
</tr>
<tr>
<td>• Cyanosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular system:</td>
<td>0</td>
</tr>
<tr>
<td>• No signs/symptoms</td>
<td>1</td>
</tr>
<tr>
<td>• HR 100-125 BPM, palpitations, generalized weakness, benign dysrhythmia, or hypotension</td>
<td>2</td>
</tr>
<tr>
<td>• HR &gt;125 BPM, or hypotension with SBP &lt;90 mmHg, malignant dysrhythmia, or cardiac arrest</td>
<td>3</td>
</tr>
<tr>
<td>Local wound:</td>
<td>0</td>
</tr>
<tr>
<td>• No signs/symptoms</td>
<td>1</td>
</tr>
<tr>
<td>• Pain, swelling, or ecchymosis within 5-7.5 cm of bite site</td>
<td>2</td>
</tr>
<tr>
<td>• Pain, swelling, or ecchymosis involving less than half the extremity (7.5-50 cm from bite site)</td>
<td>3</td>
</tr>
<tr>
<td>• Pain, swelling, or ecchymosis involving half to all of extremity (50-100 cm from bite site)</td>
<td>4</td>
</tr>
<tr>
<td>• Pain, swelling, or ecchymosis extending beyond affected extremity (more than 100 cm from bite site)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system:</td>
<td>0</td>
</tr>
<tr>
<td>• No signs/symptoms</td>
<td>1</td>
</tr>
<tr>
<td>• Vomiting or diarrhea</td>
<td>2</td>
</tr>
<tr>
<td>• Repeated vomiting, diarrhea, hematemesis, or hemanthecesis</td>
<td>3</td>
</tr>
<tr>
<td>Hematologic system:</td>
<td>0</td>
</tr>
<tr>
<td>• No signs/symptoms</td>
<td>1</td>
</tr>
<tr>
<td>• Coagulation parameters slightly abnormal: PT &lt;20 secs, PTT &lt;50 secs, platelets 100-150K/mL, or fibrinogen 100-150 mg/mL</td>
<td>2</td>
</tr>
<tr>
<td>• Coagulation parameters abnormal: PT &gt;20-25 secs, PTT &gt;50-75 secs, platelets 50-100K/mL, or fibrinogen 50-100 mg/mL</td>
<td>3</td>
</tr>
<tr>
<td>• Coagulation parameters markedly abnormal: with serious bleeding or the threat of spontaneous bleeding, unmeasurable PT or PTT, platelets &lt;50K/mL, undetectable fibrinogen, severe abnormalities of other laboratory values also fall into this category</td>
<td>4</td>
</tr>
<tr>
<td>Central nervous system:</td>
<td>0</td>
</tr>
<tr>
<td>• No signs/symptoms</td>
<td>1</td>
</tr>
<tr>
<td>• Minimal apprehension, headache, weakness, dizziness, chills, or paralysis</td>
<td>2</td>
</tr>
<tr>
<td>• Moderate apprehension, headache, weakness, dizziness, chills, parathesias, confusion, or fasciculations in area of bite site</td>
<td>3</td>
</tr>
<tr>
<td>• Severe confusion, lethargy, seizures, coma, psychosis, or generalized fasciculations</td>
<td>3</td>
</tr>
</tbody>
</table>

Max score of 20

Appendix B. Weant, et al. Treatment Algorithm

- Minimal Envenomation
  - Observe patient for signs and symptoms of progression of envenomation syndrome
  - Progression of envenomation
    - No
      - No antivenin treatment necessary
    - Yes
      - Monitor for signs and symptoms of progression of envenomation syndrome
      - Envenomation progression?
        - No
          - No further treatment necessary
        - Yes
          - Repeat 4-6 vial dose
- Moderate Envenomation
  - Initial FabAV dose of 4 vials (see preparation below)
  - Initial Response/Control
    - Yes
      - No further treatment necessary
    - No
      - Repeat 4-6 vial dose
- Severe Envenomation
  - Initial FabAV dose of 4 vials (see preparation below)
  - Initial Response/Control
    - Yes
      - Maintenance Dosing: 2 vials q4hrs x 3 dose at 6hr, 12hr, 18hr post-load
    - No further treatment necessary