Complimentary CME/CE/CPE

Time Is of the Essence: Assessment and Management Updates for Patients Presenting With Snake Envenomation

Provided by

Med-IQ

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

Gold BS, et al. *N Engl J Med*. 2002;347:347-56.

North American Pit Vipers

- Rattlesnakes
  - *Crotalus*

North American Pit Vipers

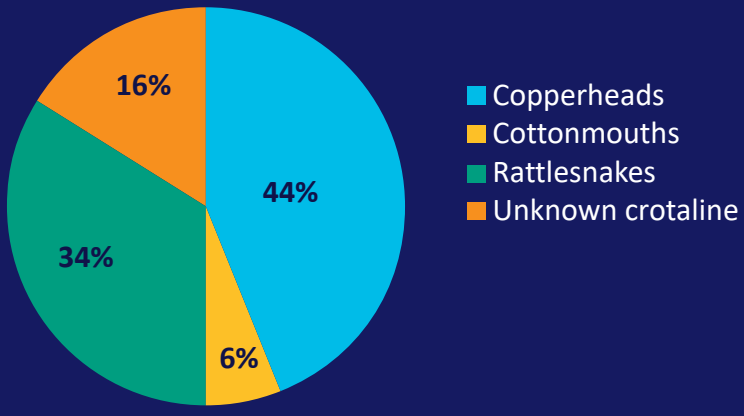
- Pygmy rattlesnakes
  - *Sistrurus*

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]



1. O'Neil ME, et al. *Wilderness Environ Med*. 2007;18:281-7;
2. Gummin DD, et al. *Clin Toxicol*. 2017;55:1072-252;
3. Seifert SA, et al. *Clin Toxicol (Phila)*. 2009;47:327-35.

Pit Viper Venom

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

Norris RL, et al. Bites by Venomous Reptiles in Canada, the United States, and Mexico. In: Auerbach PS, et al, eds. *Auerbach's Wilderness Medicine*. 7th ed. Philadelphia; 2017. p. 729-60.

Venom Effects

- Venom effects
  - Tissue injury
  - Hematologic
  - Systemic
    - Cardiovascular
    - Neurologic
    - Gastrointestinal
    - Pulmonary
    - Renal

Gold BS, et al. *N Engl J Med*. 2002;347:347-56; Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

Local Tissue Effects

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

Lavonas E, et al. *BMC Emerg Med*. 2011;11:2.

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

1. Guitierrez JM, et al. *Toxicon*. 2009;57:976-87;
2. McCleary RJ, et al. *Thromb Res*. 2013;132:642-6.

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

Gold BS, et al. *N Engl J Med*. 2002;347:347-56; Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

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

Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

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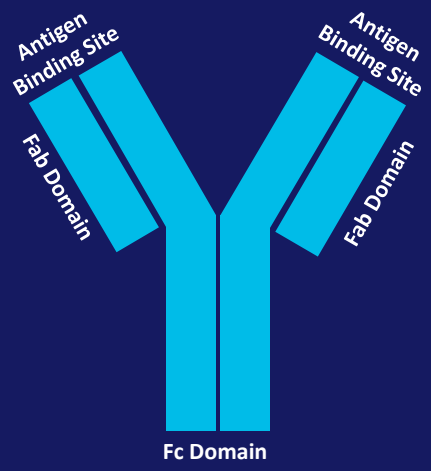
Antivenoms

- 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



Gold BS, et al. *N Engl J Med*. 2002;347:347-56.

Pit Viper Antivenoms

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

1. US FDA. www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/UCM277363.pdf;
2. US FDA. www.fda.gov/downloads/BloodBloodProducts/ucm117573.pdf;
3. US FDA. www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM446175.pdf.

Antivenom Therapy: Indications*

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

*Based on Lavonas et al. 2011 algorithm and pertains to antivenom/CroFab only.

Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2;
US FDA. hwww.fda.gov/downloads/BloodBloodProducts/ucm117573.pdf

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]

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

1. Gerardo CJ, et al. *Ann Emerg Med*. 2017;70:223-44;
2. Anderson VE, et al. [Abstract] *Clin Toxicol*. 2017;55:692;
3. Gerardo CJ, et al. *Clin Toxicol (Phila).* 2017;55:109-44;
4. Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2;
5. Crotalidae Immune F(ab')2 [package insert]. Rare Disease Therapeutics, Inc; Franklin, TN 2018.
6. Bush SP, et al. *Clin Toxicol (Phila)*. 2015;53:37-45.

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

1. Schaeffer TH, et al. *Acad Emerg Med*. 2012;19:121-3.

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

1. Schaeffer TH, et al. *Acad Emerg Med*. 2012;19:121-31.

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

1. Scharman EJ, et al. *Ann Emerg Med*. 2001;38:55-61;
2. Lavonas EJ, et al. *Ann Emerg Med*. 2011;57:128-37;
3. Yin S, et al. *Acad Emerg Med*. 2011;18:46-52;
4. Seifert SA, et al. *Clin Toxicol*. 2009;47:327-35;
5. Thorson A, et al. *J Toxicol Clin Toxicol*. 2003;41:29-35;
6. Lavonas EJ, et al. *Ann Emerg Med*. 2008;52:S141-2.

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

1. Gerardo CJ, et al. *Clin Toxicol (Phila)*. 2017;55:109-14;
2. Gerardo CJ, et al. *Ann Emerg Med*. 2017;70:223-44.

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

Gerardo CJ, et al. *Ann Emerg Med*. 2017;70:233-44.

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 signficant[2,3]
- Treatment-related adverse effects: 36% FabAV vs 10% placebo[1]

1. Gerardo CJ, et al. *Ann Emerg Med*. 2017;70:233-44;
2. Gerardo CJ, et al. Abstract presented at Venom Week VI. Kingsville, TX, 2018;
3. Lavonas EJ, et al. *BMC Emerg Med*. 2015;15:9.

Results: Additional Outcomes

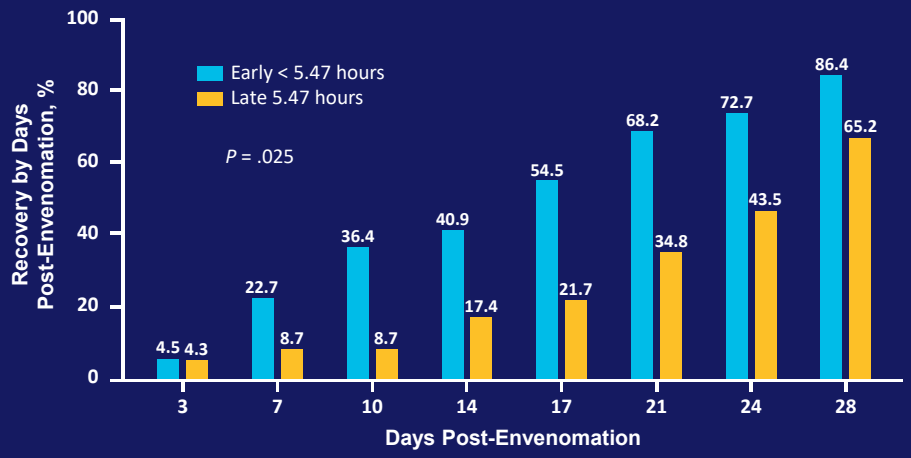
- Routinely favored FabAV vs. placebo: DASH, LEFS, grip strength, NPRS, PROMIS PF-10[1]
- Opioid analgesic use[2]
  - Placebo group was 5.5 times more likely to be on opioids during recovery than the antivenom group

Day	Opioid Use (FabAV) (%)	Opioid Use (Placebo) (%)	Difference (%)
3	34.1	42.9	8.8
7	27.3	39.3	12.0
10	11.4	28.6	17.2
14	4.5	25.0	20.5
17	4.5	25.0	20.5
21	0.0	14.3	14.3
24	0.0	10.7	10.7
28	0.0	7.1	7.1

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

1.Gerardo CJ, et al. *Ann Emerg Med*. 2017;70:233-244.
2. Freiermuth C, et al. Abstract presented at Venom Week VI. 2018. Manuscript submitted.

Recovery by Time to Treatment Fab Antivenom Group



Anderson VE, et al. Abstract presented at North American Congress of Clinical Toxicology (NACCT). *Clin Toxicol*. 2017;55:692. Manuscript in Review.

Pros/Cons of Treating Copperhead and/or Mild Envenomation

Pro	Con
• Presenting severity is not final severity – Risk of progression • Safety • Efficacy – Recovery of function – Pain – Quality of life	• Cost • Most recover

New axiom "offer Fab antivenom if symptomatic"

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Prehospital[1,2]

Do's	Don'ts
• ABCs	• Cut
• Reassure patient	• Suction
– Stay calm	• Ice
• Transport	• Use electricity
• Position extremity	• Use tourniquets
	• Use compression
	• Panic

1. Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2;
2. Kanaan NC, et al. *Wilder Environ Med*. 2015;26:472-87.

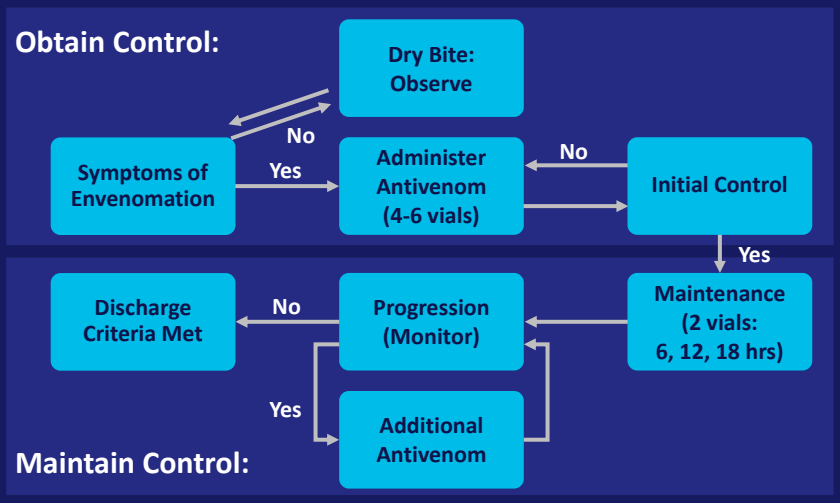
ED/Hospital Initial Care

Do's	Don'ts

• ABCs
• Assess patient
• Offer reassurance
• Call expert
• Update tetanus
• Control pain
• Properly position
  – Elevate once antivenom is given
• *Antivenom algorithm**
	• NSAIDs?
	• Steroids
	• Fasciotomy
	  – Prophylactically
	  – Without antivenom
	  – Without compartment pressures

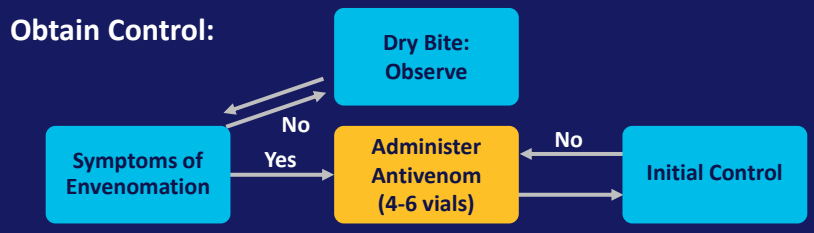
*Modified adaption of Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

Fab Antivenom Algorithm Goals: Obtain and Maintain Control



Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

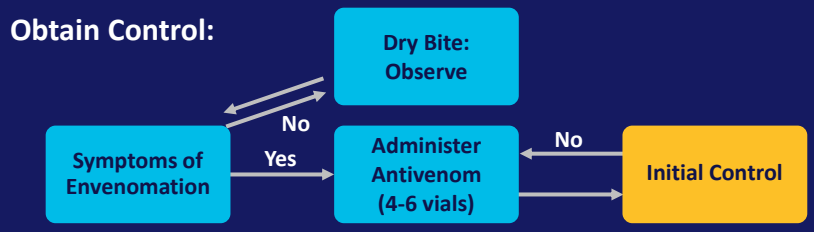
Fab Antivenom Algorithm Goals: Obtain and Maintain Control



- Offer vs administer
  - Mild vs moderate/severe
  - Most progress[1]
  - Time is tissue
- Choose initial dose
  - Assess risk factors for severity
  - Example: children, hand, presenting severity, etc.

Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2;
1. Gerardo CJ, et al. *Acad Emerg Med*. 2015;22:308-14.

Fab Antivenom Algorithm Goals: Obtain and Maintain Control



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

Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

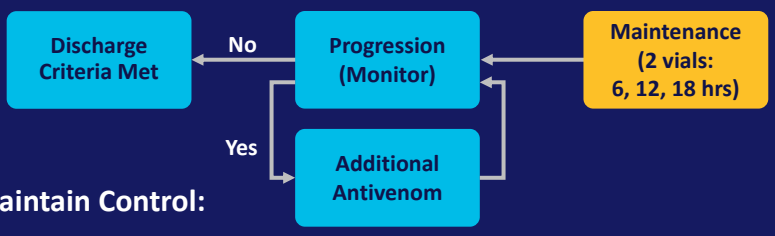
Assessing Severity/Progression

- 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

Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

Fab Antivenom Algorithm Goals: Obtain and Maintain Control

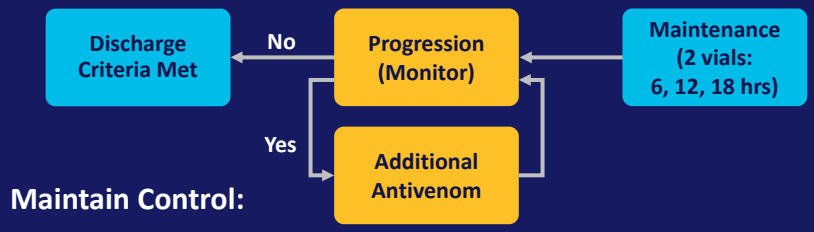
- Do all patients require maintenance?
- Options:
  - Most mild/moderate patients receive ~10 vials[1]
  - Administer as needed
  - Scheduled



1. Gerardo CJ, et al. *Acad Emerg Med*. 2015;22:308-14;
Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

Fab Antivenom Algorithm Goals: Obtain and Maintain Control

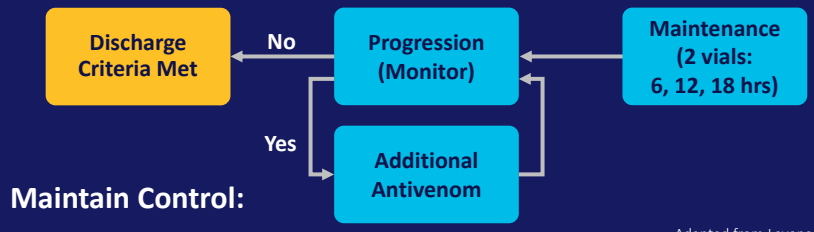
- How frequently should I reevaluate the patient?
- Differentiating progressive tissue symptoms vs redistribution of fluid due to gravity
- Absolute lab number vs trend



Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

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



Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

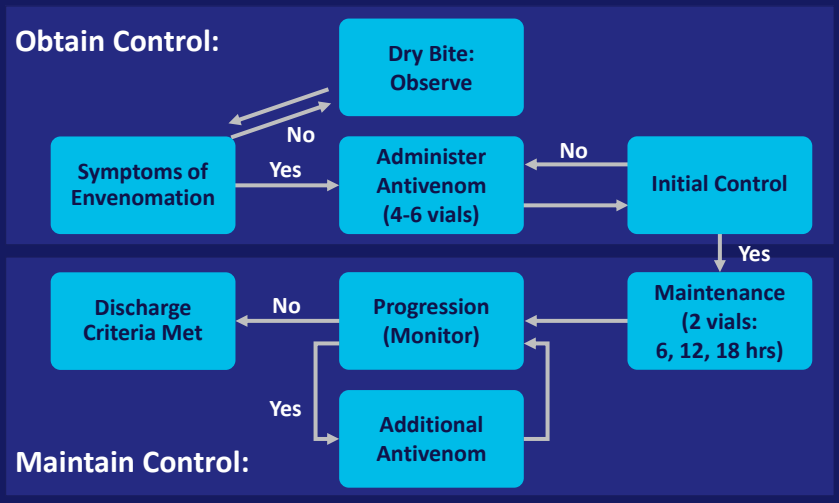
Case Discussions

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

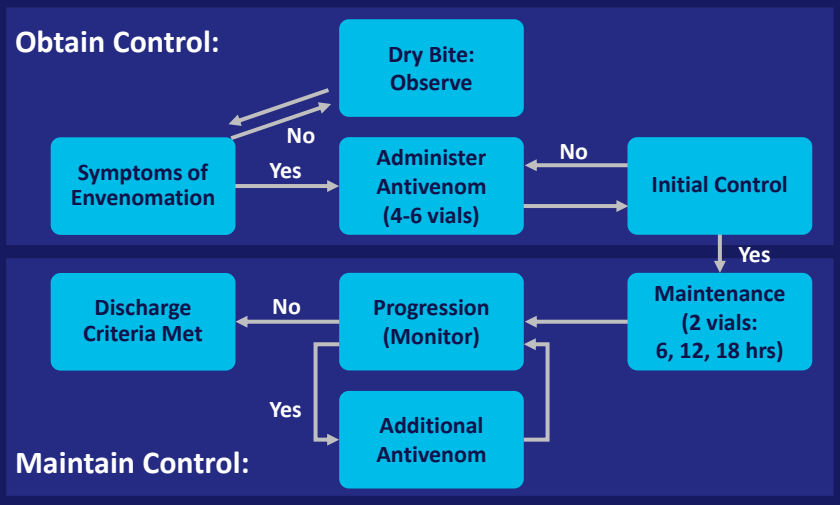


Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

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

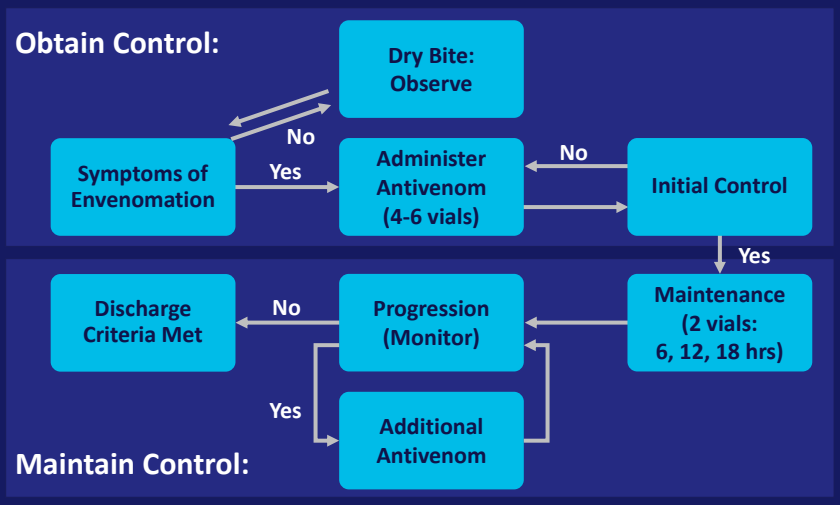


Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

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



Adapted from Lavonas EJ, et al. *BMC Emerg Med*. 2011;11:2.

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

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