



HEALTHTRUST[®]
UNIVERSITY CONFERENCE

Tuesday, July 28, 2021

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

Keith J. Boesen, PharmD & Nicholas B. Hurst, M.D., MS

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

Audience Poll Question: #1 of 5

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 SSSKILLED SSSNAKEBITE SSSSPECIALIST!!!

The background of the slide is a dark blue, semi-transparent overlay. On the left side, there is a close-up of an IV drip chamber with a clear plastic reservoir and a white drip chamber, with a clear plastic tube extending downwards. The rest of the background is a blurred image of a hospital hallway with people walking, creating a sense of a clinical environment.

PIT VIPER ENVENOMATIONS

PIT VIPERS

Loreal Pits



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

Movable Fangs



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

PIT VIPERS

Loreal Pits



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

Movable Fangs



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

PIT VIPERS

Loreal Pits



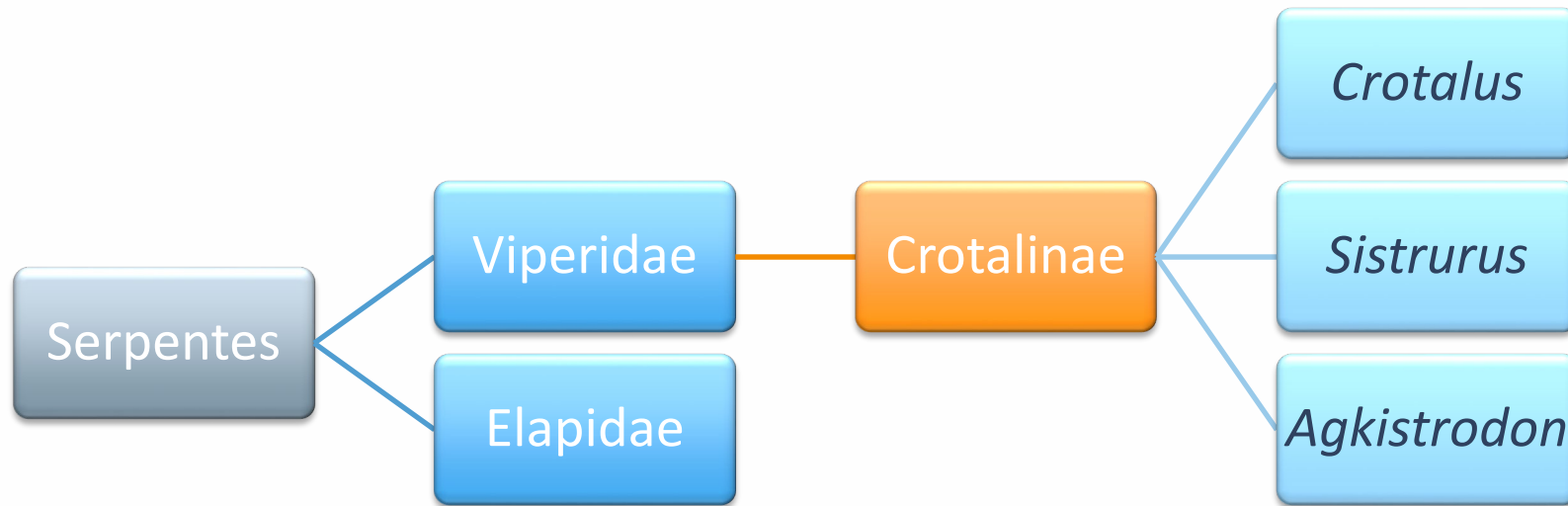
1. Russel 1983 -Photo provided by the Arizona Poison and Drug Information Center

Movable Fangs

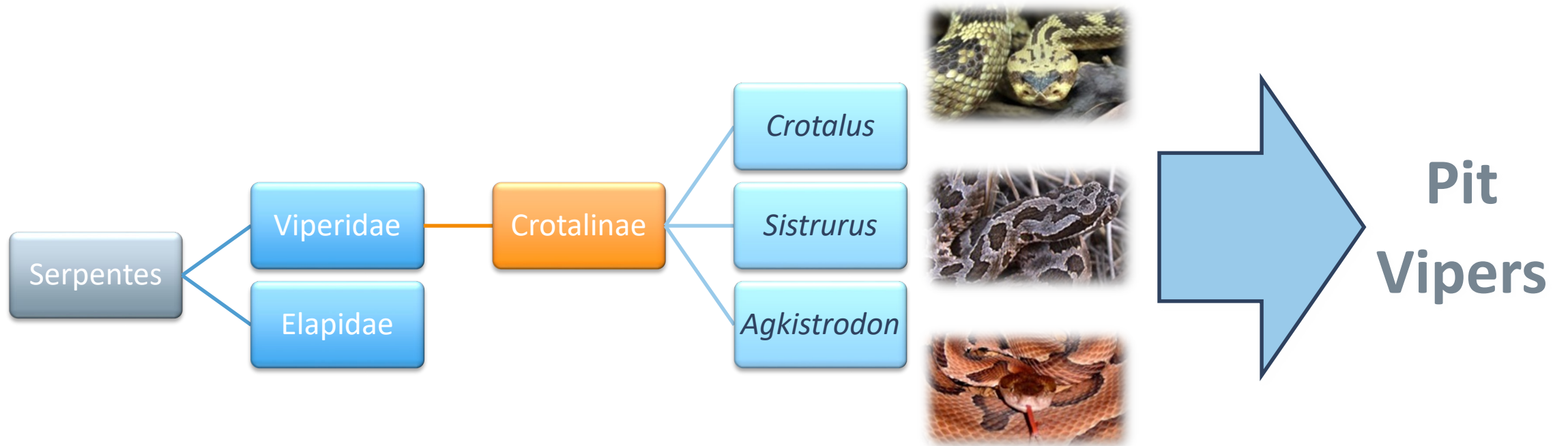


1. Russel 1983 -Photo provided by the Arizona Poison and Drug Information Center

PHYLOGENETIC TREE



PHYLOGENETIC TREE



EPIDEMIOLOGY

- U.S. Species and Subspecies = 39²
 - *Agkistrodon* = 8
 - Copperhead, Cottonmouth/Water Moccasin
 - *Sistrurus* = 6
 - Pygmy, Massasauga
 - *Crotalus* = 25
 - Rattlesnake
- Envenomations by Pit Vipers
 - U.S. Estimates: >6,000³
 - AAPCC: 4,183 in 2019⁴
 - Outcome Major: 171
 - Death: 1

2. Venombyte 2019 3. Parrish 1966 4. Gummin 2020



Audience Poll Question: #2 of 5

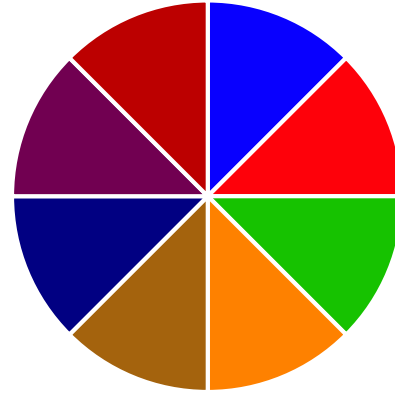
TRUE or FALSE: The exact species of Pit Viper must be known in order to determine the correct treatment for a patient who has been bitten.

- a. True
- b. False

VENOMICS

VENOMICS

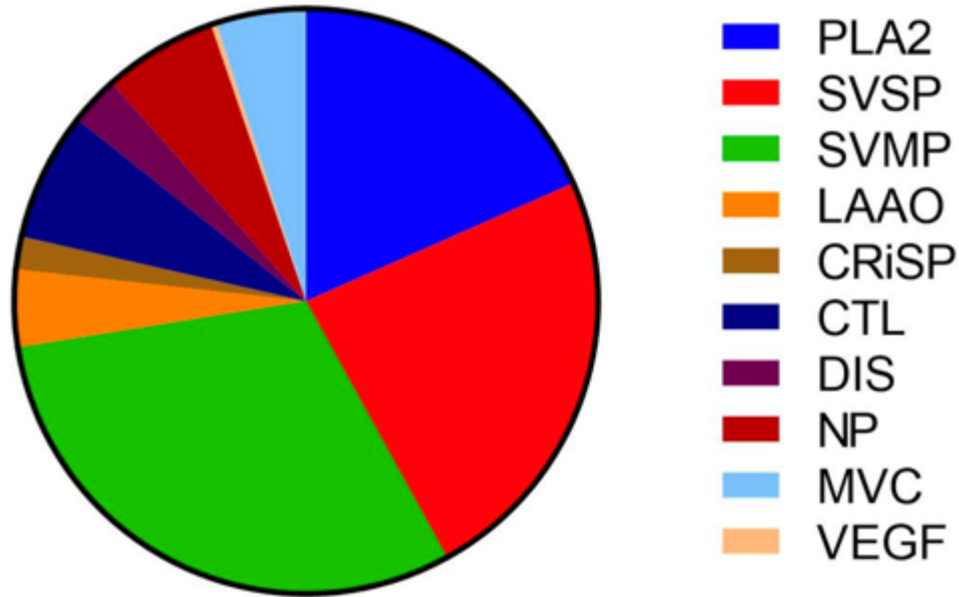
- Phospholipase A₂ - Hemolysis/Myotoxic/Neurotoxic
- SVSP - Coagulopathy/Edema/Hypotension
- SVMP - Coagulopathic/Hemorrhagic/Myonecrosis
- L-amino acid oxidase - Cytotoxic/Myotoxic
- Cysteine-Rich Secretory Proteins - Smooth Muscle Paralysis
- C-Type Lectins - Thrombocytopenia
- Disintegrins - Inhibition of Platelet Aggregation
- Peptides - Hypotension/Myotoxic



VENOMICS

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

CROTALINE (65 SPECIES)



VENOMICS

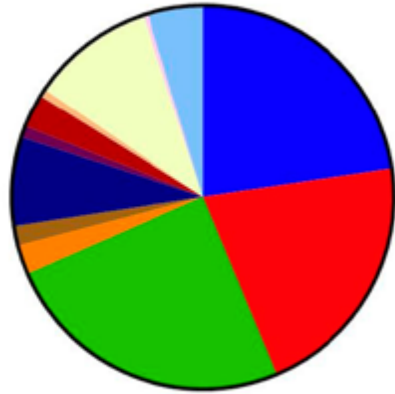
SPECIES TO SPECIES VARIATION



-Photo provided by RDT

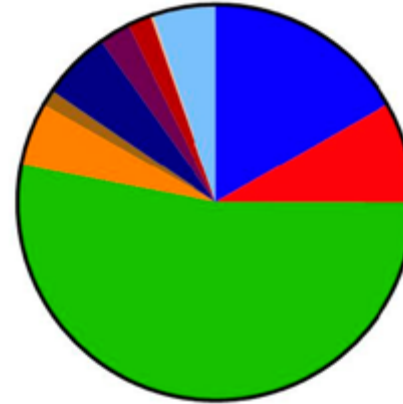
FOUR GENERA OF PIT VIPERS

Crotalus (10 species)



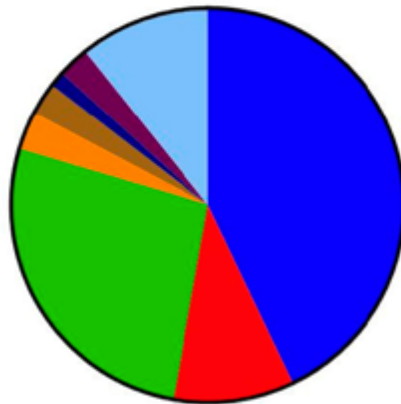
- PLA₂
- SVSP
- SVMP
- LAAO
- CRiSP
- CTL
- DIS
- NP
- VEGF
- DEF
- MPi
- MVC

Bothrops (10 species)



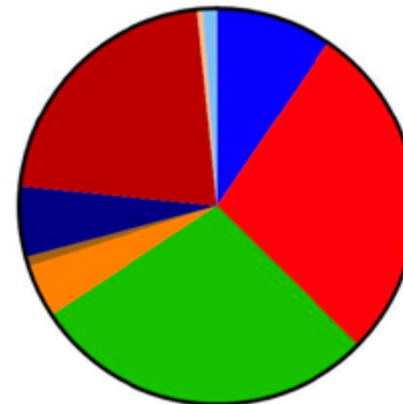
- PLA₂
- SVSP
- SVMP
- LAAO
- CRiSP
- CTL
- DIS
- NP
- VEGF
- MVC

Agkistrodon (3 species)



- PLA₂
- SVSP
- SVMP
- LAAO
- CRiSP
- CTL
- DIS
- MVC

Lachesis (4 species)

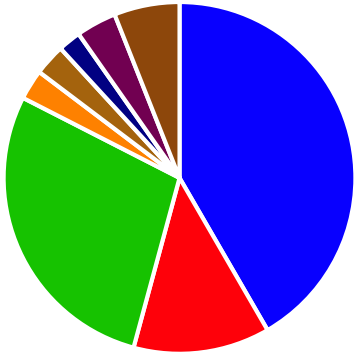


- PLA₂
- SVSP
- SVMP
- LAAO
- CRiSP
- CTL
- NP
- VEGF
- MVC

SPECIES TO SPECIES

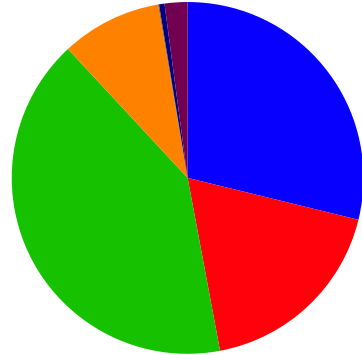
Agkistrodon

A. piscivorus



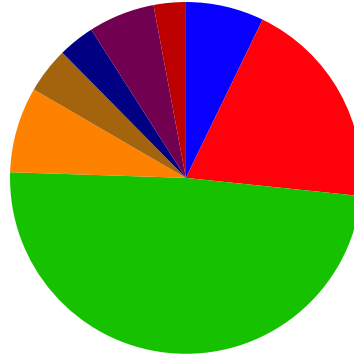
Bothrops

B. asper



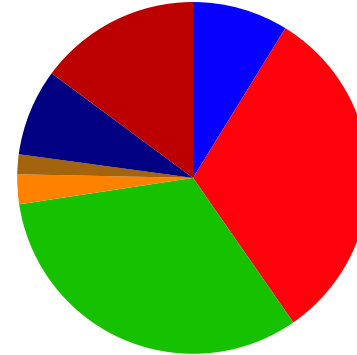
Crotalus

C. atrox



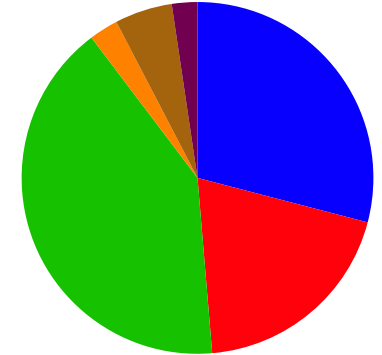
Lachesis

L. muta

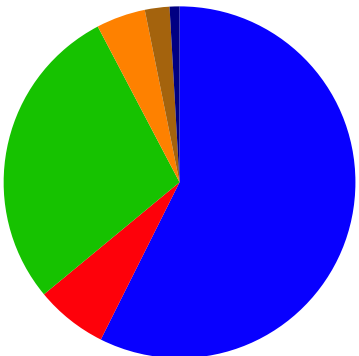


Sistrurus

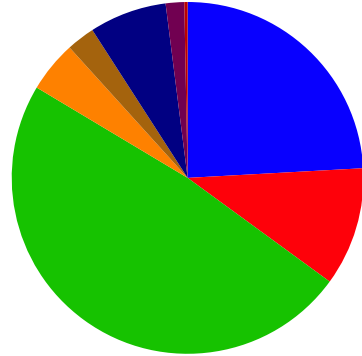
S. catenatus



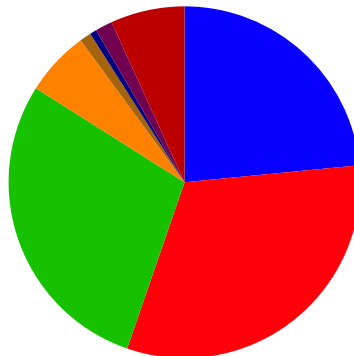
A. contortrix



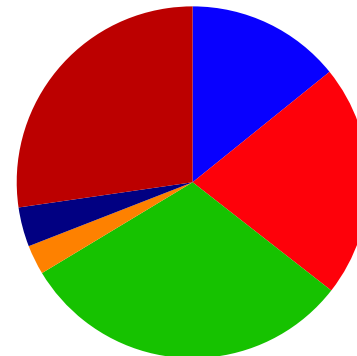
B. atrox



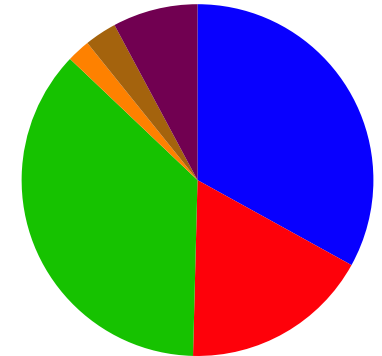
C. simus



L. stenophrys



S. miliarius



VENOMICS

INTRASPECIES VARIATION

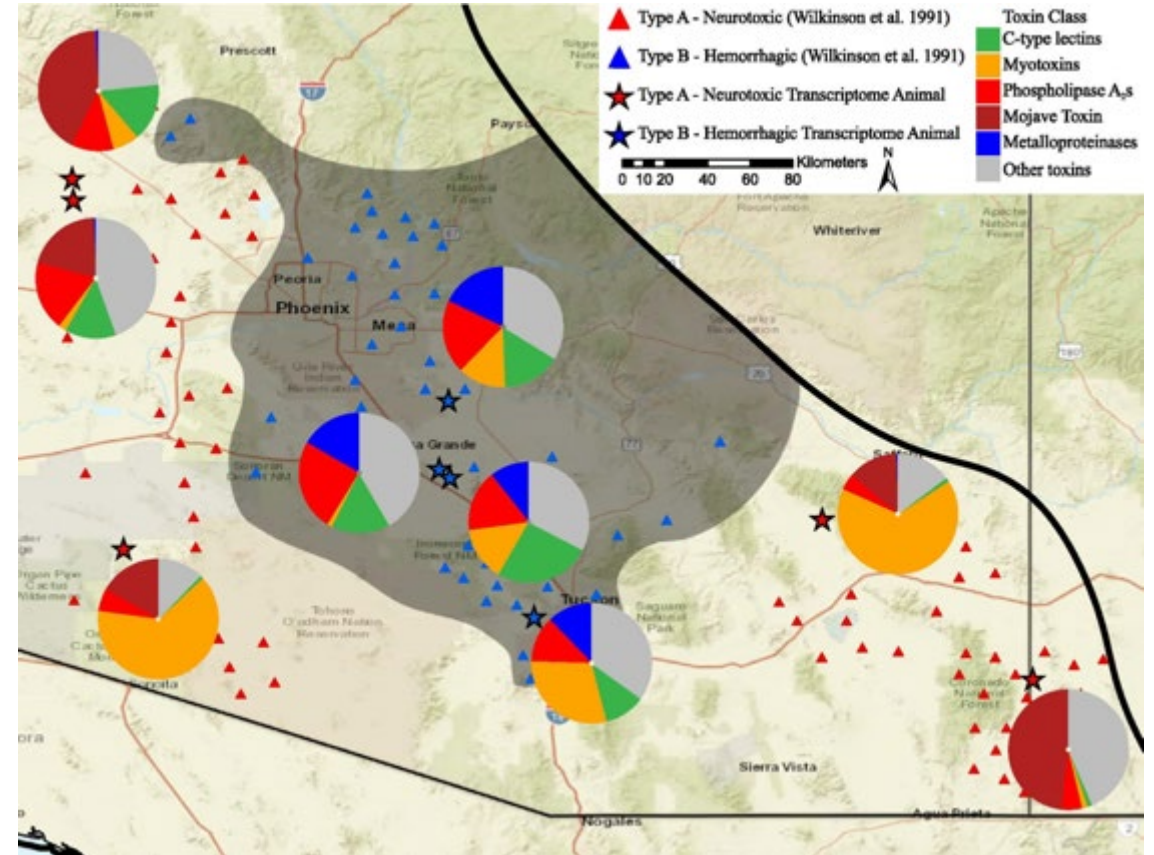
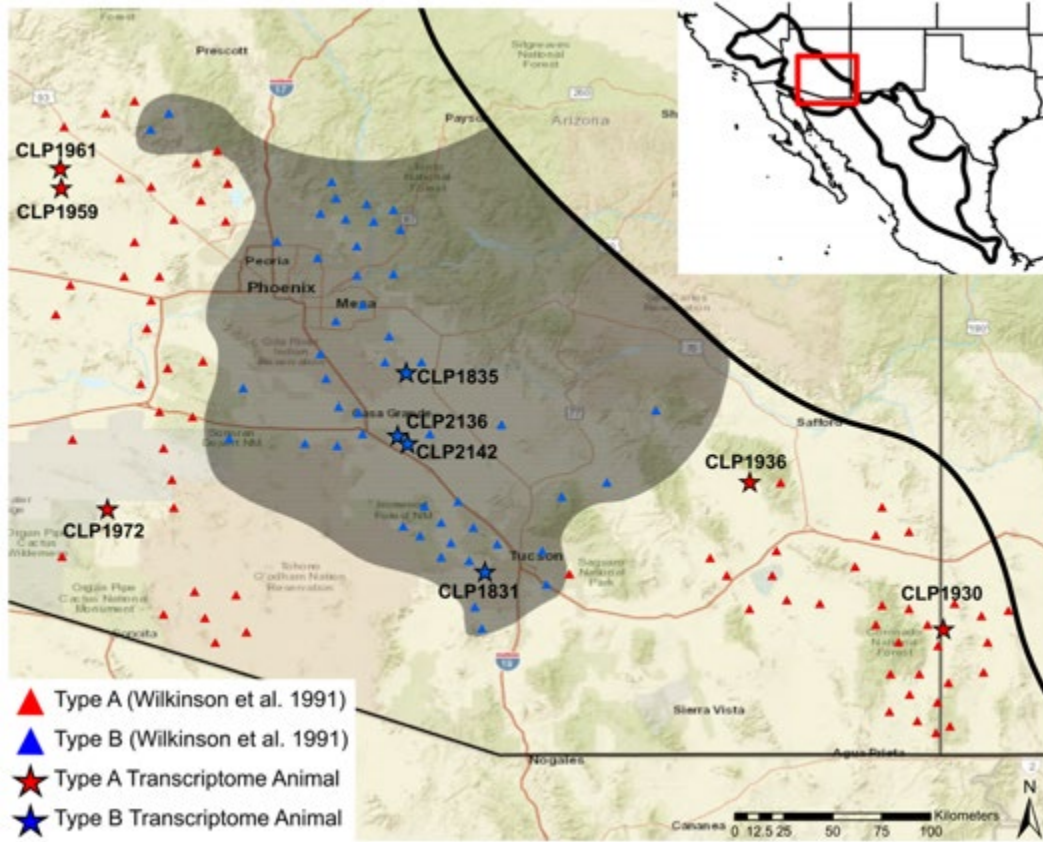


-Photo provided by RDT



Mohave Rattlesnake
(*Crotalus scutulatus*)

VENOMICS



VENOMICS

ONTOGENIC VARIATION



-Photo provided by RDT

VENOMICS

- *C. atrox*⁹
 - Juveniles > hemorrhagic toxins than Adults
- *C. simus*¹⁰
 - Newborn = Crotoxin
 - Juvenile = Less Crotoxin
 - Adult = Almost no Crotoxin
- *B. asper*¹⁰
 - Newborn > Hemorrhagic
 - Adults > Myotoxic
- Similar findings with *Crotalus godmani* and *Atropoides mexicanus*¹⁰



Audience Poll Question: #3 of 5

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

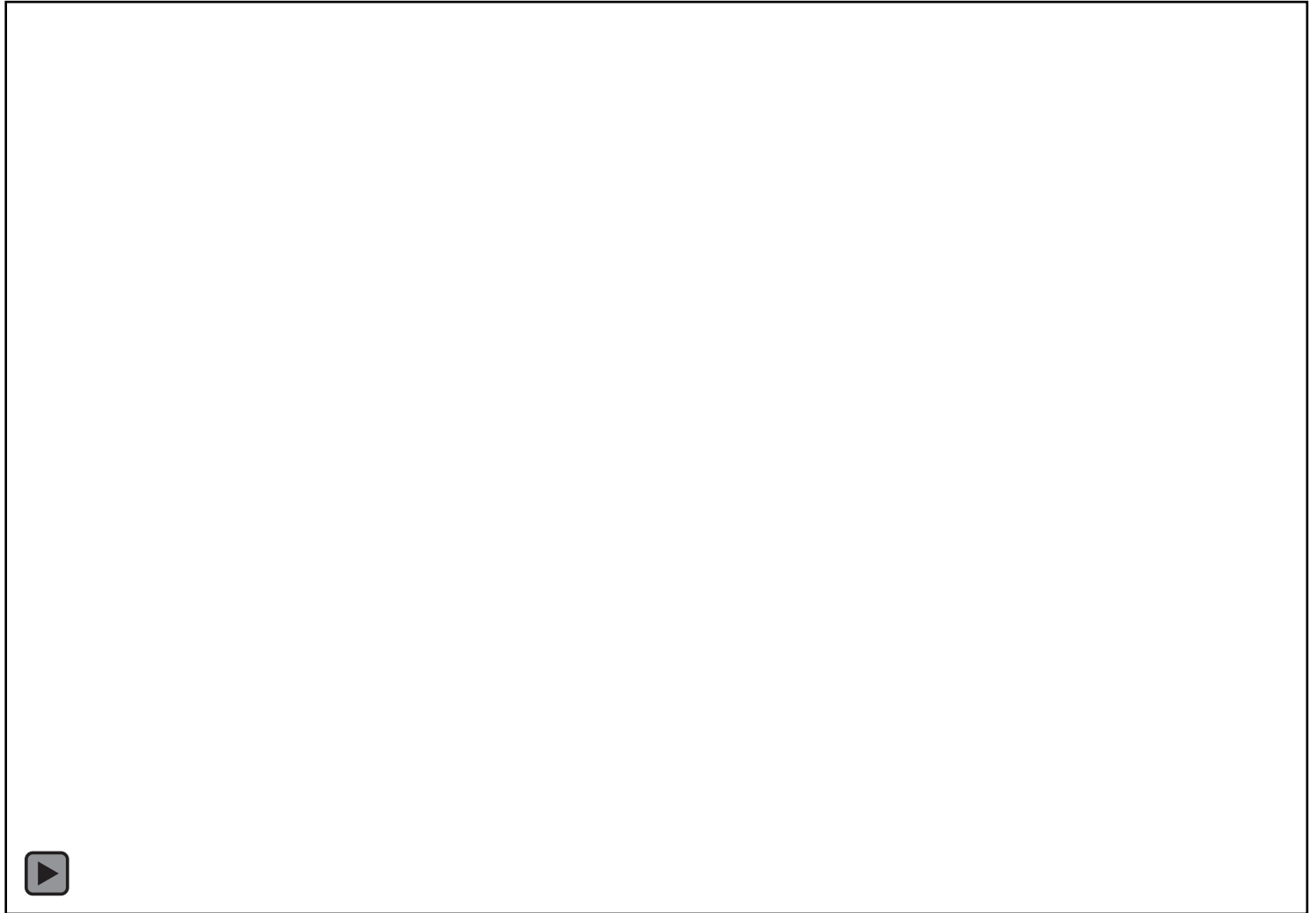


-Photo provided by the Arizona Poison and Drug Information Center

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)

11. Walter 2007

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

12. Lavonas 2014



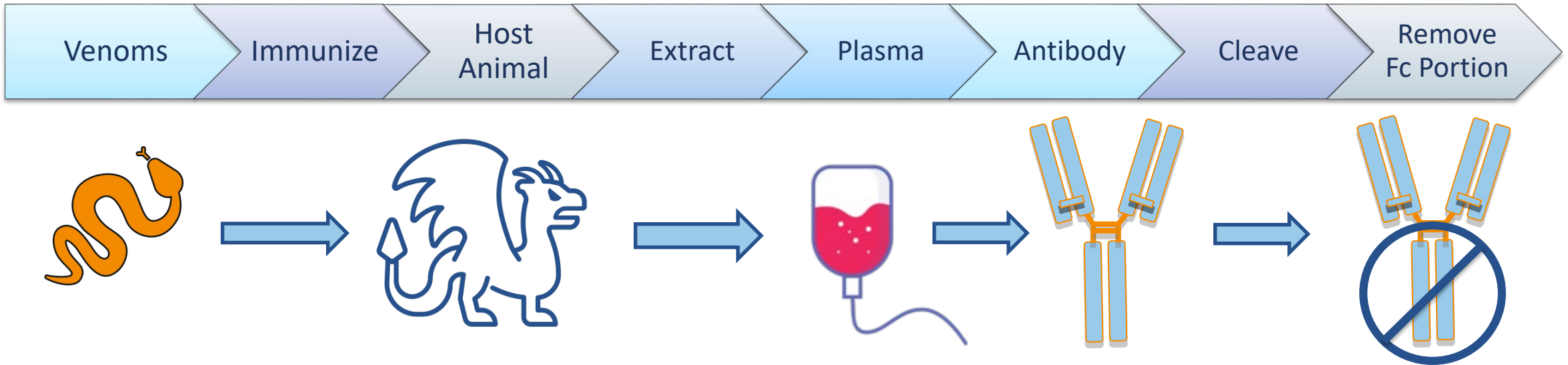
ANTIVENOM

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

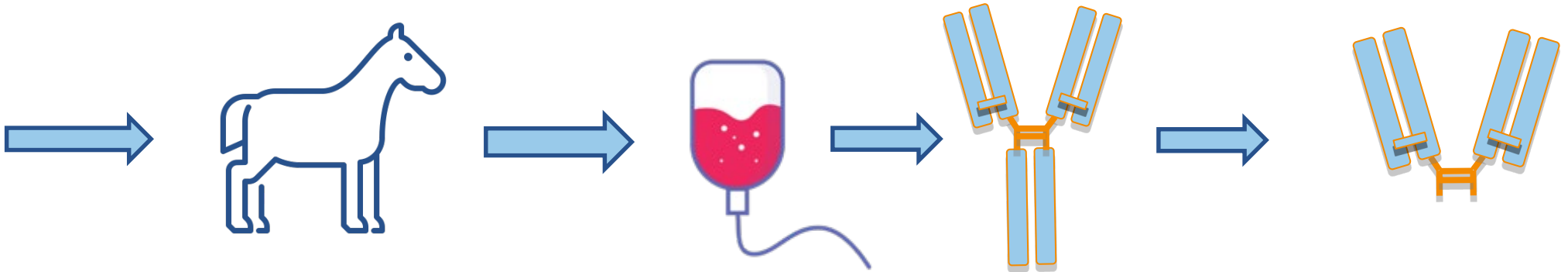
ANTIVENOM



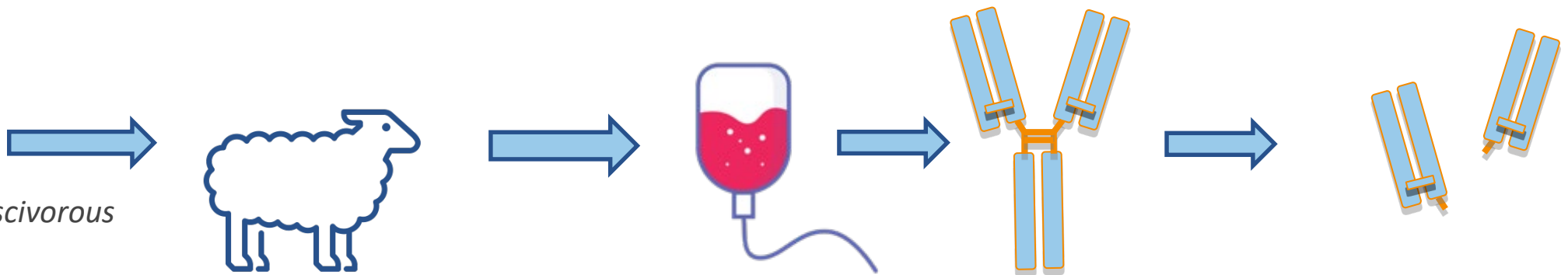
ANTIVENOM



- *Bothrops asper*
- *Crotalus simus*

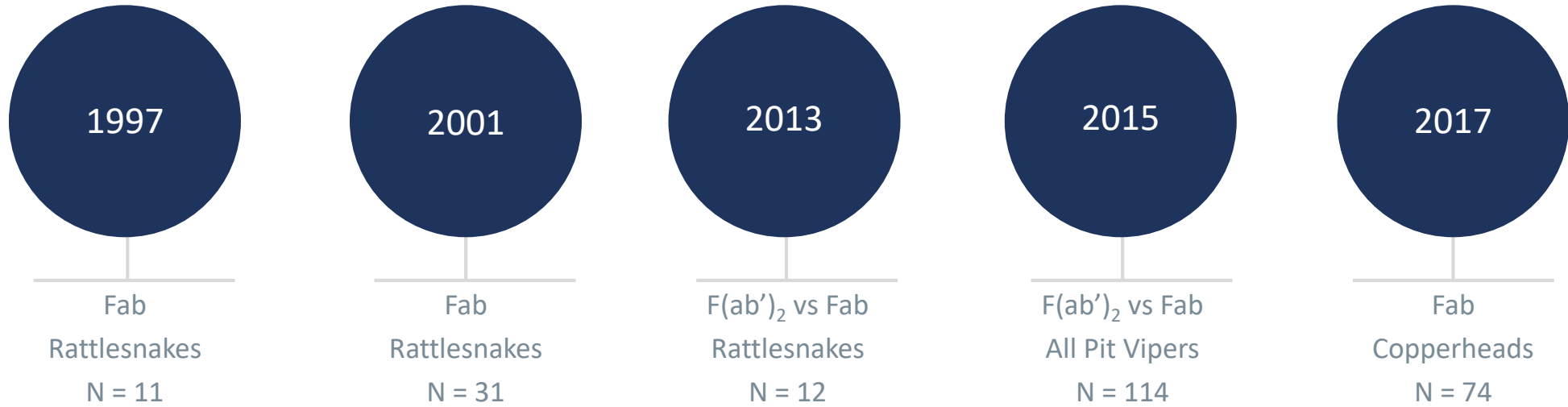


- *Crotalus atrox*
- *C. adamanteus*
- *C. scutulatus*
- *Agkistrodon piscivorous*



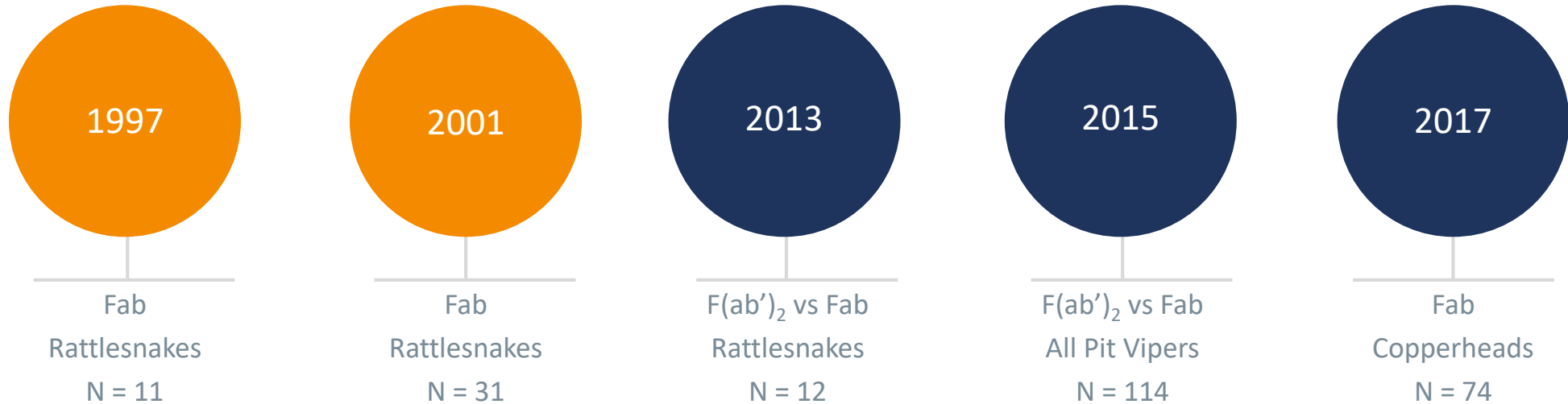
13. Lausten 2018 14. Anavip PI 2021 15. CroFab PI 2019

PROSPECTIVE ANTIVENOM RESEARCH



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

PROSPECTIVE ANTIVENOM RESEARCH



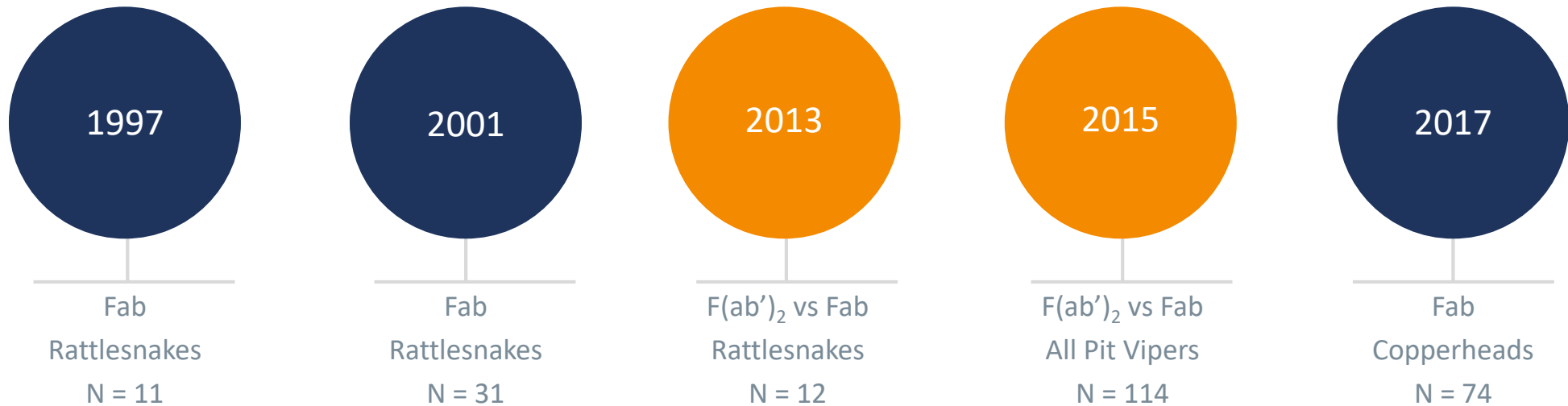
Affinity-Purified, Mixed Monospecific Crotalid Antivenom Ovine Fab for the Treatment of Crotalid Venom Poisoning.

- 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

PROSPECTIVE ANTIVENOM RESEARCH



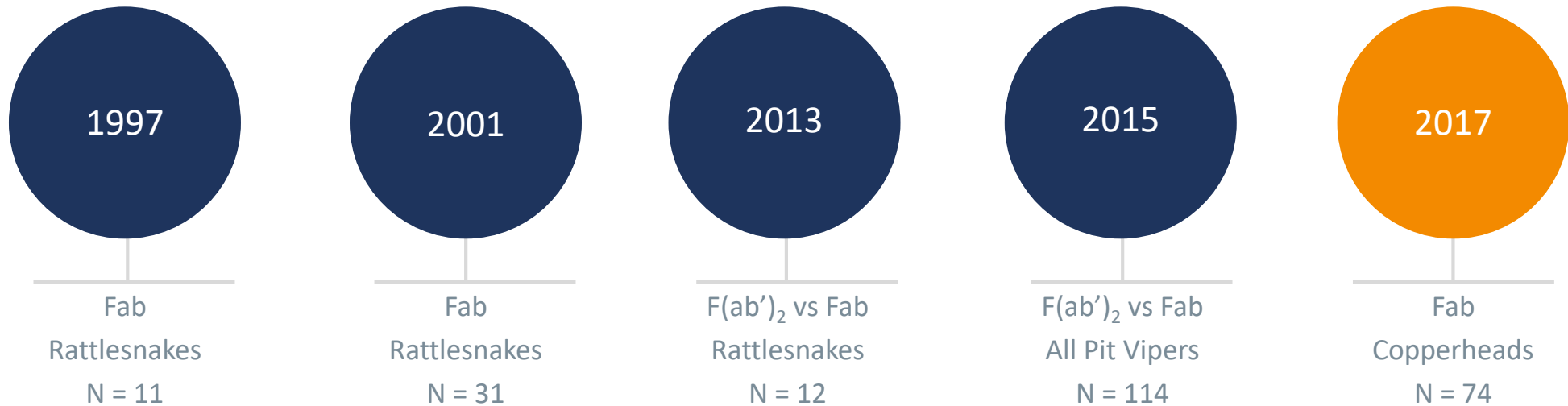
Subacute coagulopathy in a randomized, comparative trial of Fab and F(ab')₂ antivenoms

- 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

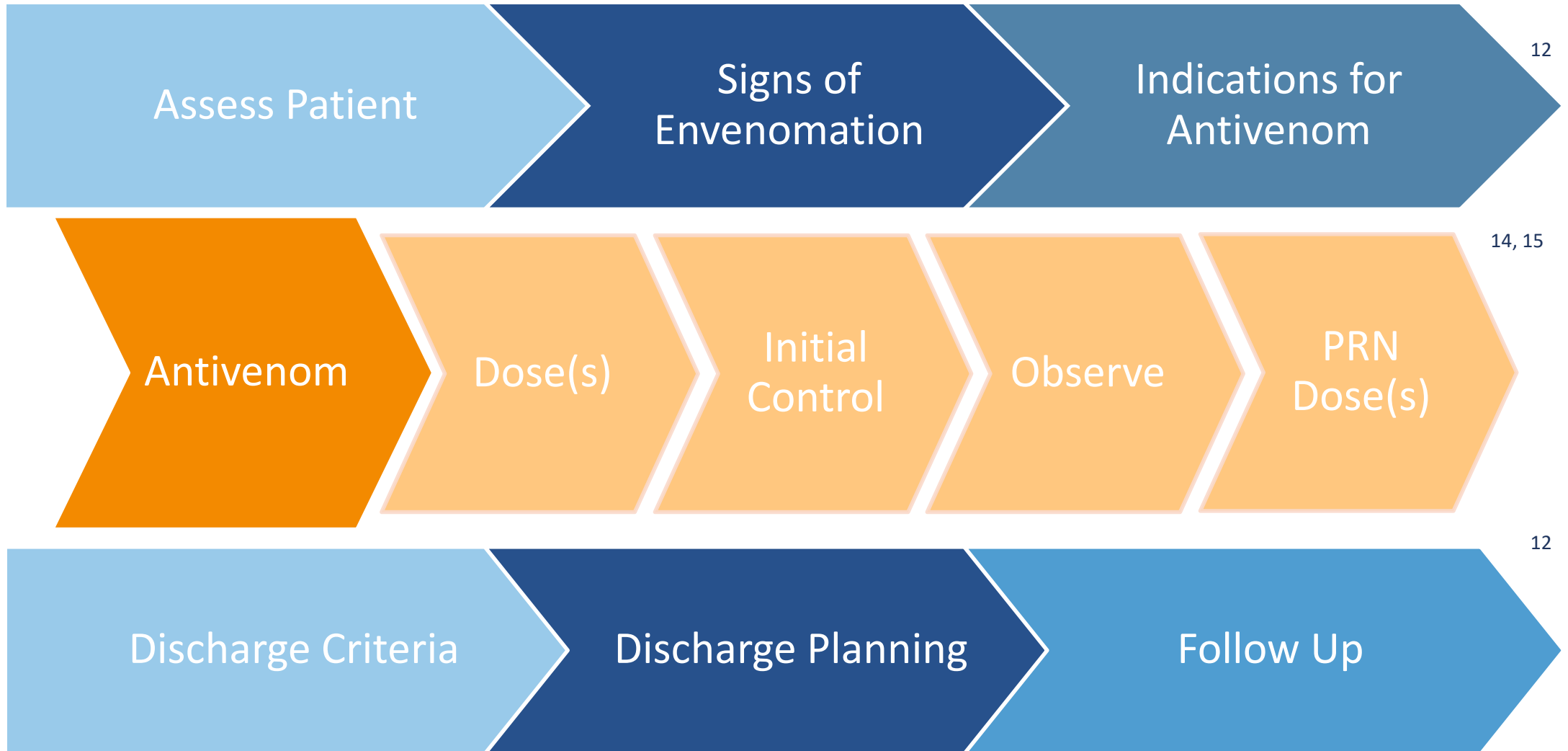
PROSPECTIVE ANTIVENOM RESEARCH



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.

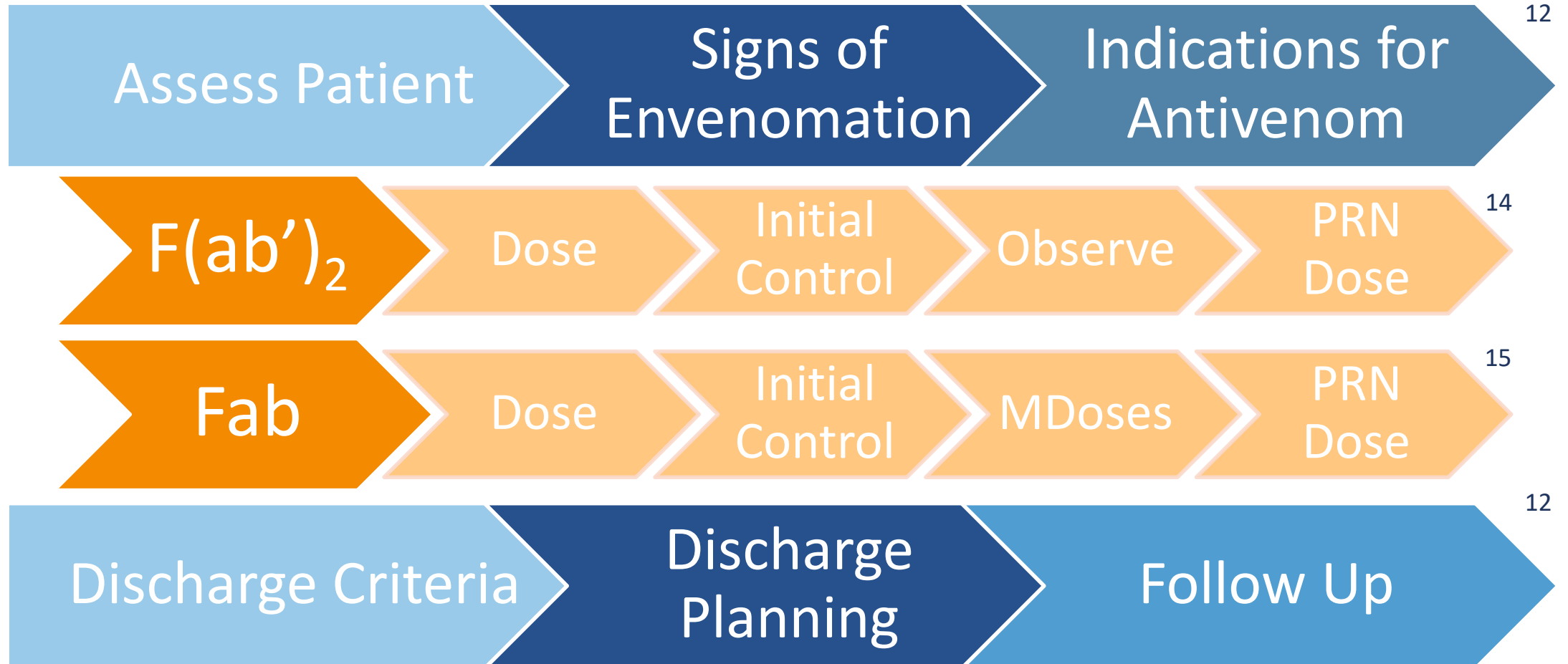
- 74 patients (45 Fab, 29 Placebo)
- Treatment with Fab reduces limb disability measured by the Patient-Specific Functional Scale 14 days after Copperhead envenomation.

COURSE OF TREATMENT



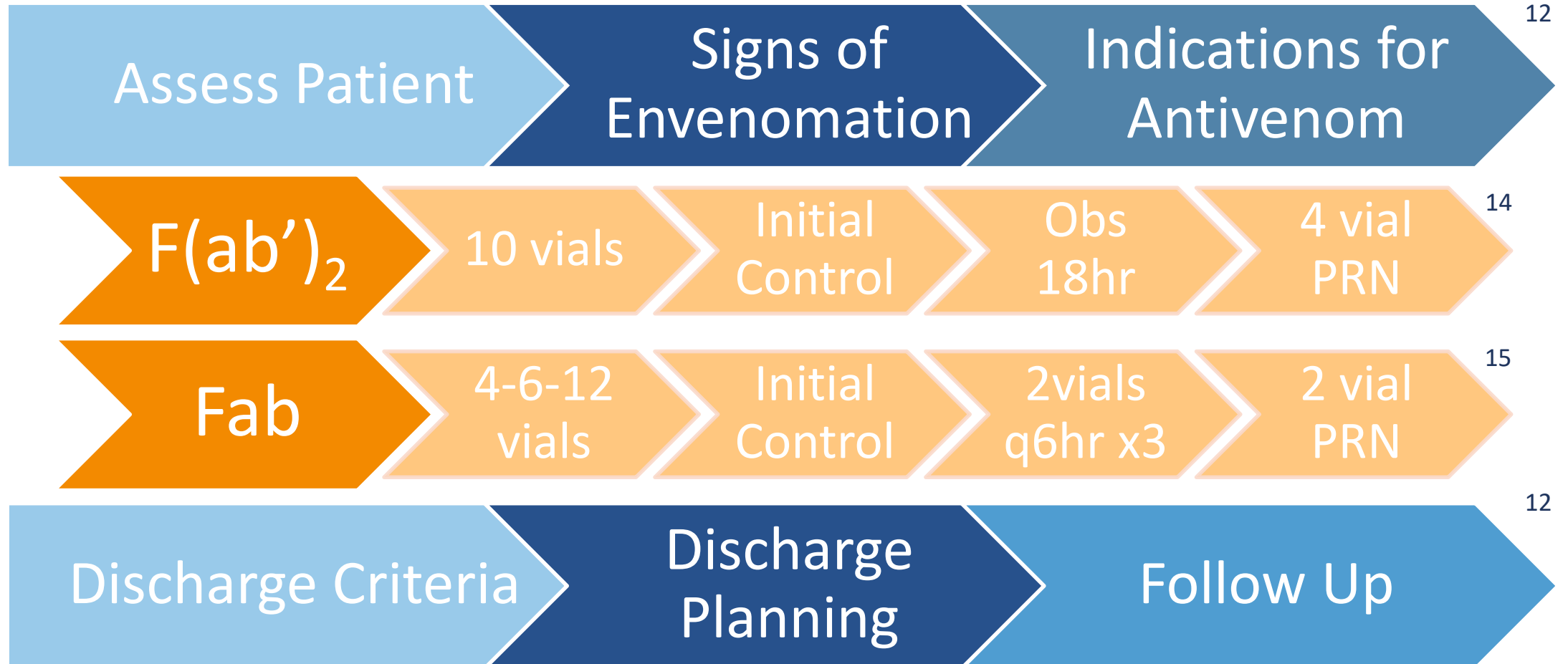
12. Lavonas 2014 14. Anavip PI 2021 15. CroFab PI 2019

COURSE OF TREATMENT



12. Lavonas 2014 14. Anavip PI 2021 15. CroFab PI 2019

COURSE OF TREATMENT



12. Lavonas 2014 14. Anavip PI 2021 15. CroFab PI 2019

PRODUCT COMPARISON PER PACKAGE INSERTS

Dosing	F(ab') ₂	Fab
Stabilizing Dose (Vials)	10	4-6-12
Maintenance Dose	None	2 vials q6h x3
Observation Time	18 hours	18 hours
PRN AV (during observation)	4 vials	2 vials
Pharmacy	F(ab') ₂	Fab
Reconstitution Time	11.8 sec (average)	No Mention
Stability after Reconstitution	6 hours	4 hours
Storage	Room Temperature	Refrigeration
Half-Life	133 hours	15 hours
Efficacy	F(ab') ₂	Fab
Initial Control	100%	98%
Late Coagulopathy	7.8%	50%

| 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.



Audience Poll Question: #5 of 5

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

1. Russell F (1983). Snake Venom Poisoning. Great Neck, New York. J.B. Lippincott Company.
2. Venombyte-2019: Snake taxonomy list last updated March 2019: http://www.venombyte.com/venom/snakes/venomous_snakes_of_the_us_by_scientific_name.asp Accessed June 2021.
3. Parrish HM, Incidence of Treated Snakebites in the United States. Public Health Reports. 1966;81(3):269-276.
4. Gummin DD, Mowry JB, Beuhler MC, et al. 2019 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th Annual Report. Clinical Toxicology. 2020;58(12):1360-1541.
5. Gutierrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite Envenoming. Nature Reviews Disease Primers. 2017;3:17063: 1-21.
6. Tasoulis T, Isbister GK, A review and database of snake venom proteomes. Toxins. 2017;9:290-312.
7. Massey DJ, Calvete JJ, Sanchez EE. Venom variability and envenoming severity outcomes of *Crotalus scutulatus scutulatus* (Mojave rattlesnake) from Southern Arizona. J of Proteomics 2012; 75:2576-2587.
8. Strickland JL, Mason AJ, Rokyta DR, Parkinson CL. Phenotypic Variation in Mojave Rattlesnake (*Crotalus scutulatus*) Venom Is Driven by Four Toxin Families. Toxins. 2018; 10(4):135. <https://doi.org/10.3390/toxins10040135>.
9. Minton SA, Weinstein SA. Geographic and Ontogenic Variation in Venom of the Western Diamondback Rattlesnake (*Crotalus atrox*). Toxicon. 1986. 24(1):71-80.
10. Lamonte B, Fernandez J, Sanz L, Angulo Y, Sasa M, Gutierrez JM, Calvete JJ. Venomous snakes of Costa Rica: Biological and medical implications of their venom proteomic profiles analyzed through the strategy of snake venomomics. J Proteomics. 2014; 105:323-339.
11. Walter FG, Chase PB, Fernandez MC, McNally J: North American Crotalinae Envenomation. Haddad and Winchester's clinical management of poisoning and drug overdose. Elsevier 2007. 4th ed.
12. Lavonas EJ, Khatri V, Daugherty C, Buchner-Bartelson B, King T, Dart R. Medically Significant Late Bleeding After Treated Crotaline Envenomation: A Systematic Review. Anals of Emergency Medicine. 2014;63(1):71-78.
13. Lausten AH, Gutierrez JM, Knudsen C, et al. Pros and cons of different therapeutic antibody formats for recombinant antivenom development. Toxicon. 2018;146:151-175.
14. Anavip [Package Insert]. DailyMed, 2021.
15. CroFab [Package Insert]. DailyMed 2019.
16. Dart RC, Seifert SA, Carroll L, et al. Affinity-purified, mixed monospecific crotalid antivenom ovine Fab for the treatment of crotalid venom poisoning. Ann Emerg Med. 1997;30(1):33-9.
17. Dart RC, Seifert SA, Boyer LV, et al. A Randomized Multicenter Trial of Crotalinae Polyvalent Immune Fab (Ovine) Antivenom for the Treatment for Crotaline Snakebite in the United States. Arch Inter Med. 2001; 161(16):2030-6.
18. Boyer LV, Chase PB, Degan JA, et al. Subacute coagulopathy in a randomized, comparative trial of Fab and F(ab')₂ antivenoms. Toxicon. 2013;74:101-8.
19. Bush SP, Ruha AM, Seifert SA, et al. Comparison of F(ab')₂ versus Fab antivenom for pit viper envenomation: A prospective, blinded, multicenter, randomized clinical trial. ClinTox 2015;53:37-45.
20. Gerardo CJ, Quackenbush E, Lewis B, et al. The Efficacy of Crotalidae Polyvalent Immune Fab (Ovine) Antivenom Versus Placebo Plus Optional Rescue Therapy on Recovery from Copperhead Snake Envenomation: A randomized, Double-Blinded, Placebo-Controlled, Clinical Trial. Annals of Emergency Medicine. 2017: 70(2):233-244.

Thank you...

Keith J. Boesen, PharmD
kboesen@raretx.com

Nicholas B. Hurst, M.D., MS
nhurst@raretx.com

Take advantage of these valuable member resources

- Clinical Evidence Reviews
- Product Feature Summaries & Technology Reviews
- Clinical Question Documents
- Conversion Guides
- Live & On-demand Webinars
- Annual HTU Conference Education
- *The Source* magazine
- 10-Spot Video Recordings
- Collaborative Summits & Communities
- Service Line Consulting & Toolkits
- Innovation Center



Questions or more info:
clinical.research@healthtrustpg.com

www.healthtrustpg.com/clinical-resources/

All-member access to resources designed for clinical integration product discussions between facility supply chain leaders & clinicians

www.healthtrustpg.com/education

All-member access to live and on-demand education opportunities, in a variety of disciplines, throughout the year

www.healthtrustpg.com/thesource/

24/7 online access to HealthTrust's member magazine, *The Source*. Also published quarterly in print format

www.healthtrustpg.com/healthtrust-innovation-center

Members can invite suppliers with new technology to submit their innovative products for review

