Envenomations

Board Review 7/11/19

What family of snakes are most commonly responsible for envenomations in the USA?

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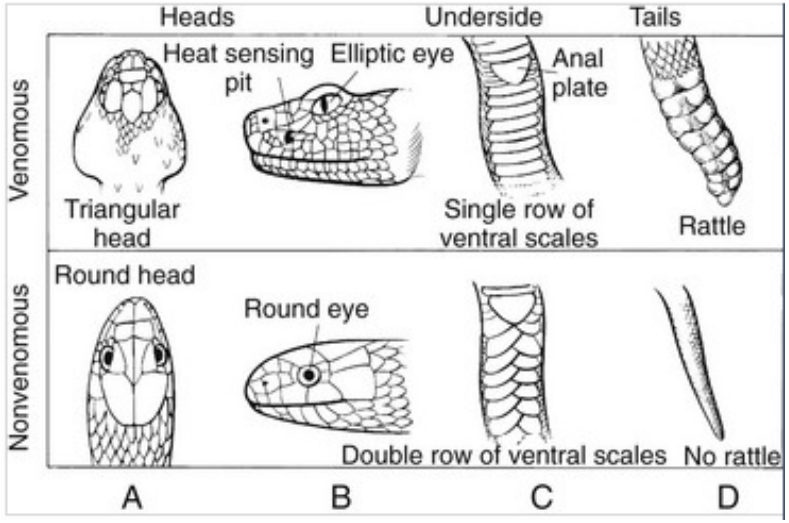
- Crotalinae
- Pit Vipers include rattlesnakes (Crotalus spp.), copperheads and water moccasins (Agkistrodon spp.), and pygmy rattlesnakes and massasaugas (Sistrurus spp.)
- Pit vipers account for 99% of venomous bites sustained in the USA
- There are apx 150,000 pit viper snakebites in dogs and cats in the USA yearly
- Southeast, western and golf coast states



Which snake is venomous?

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Coral snake (Elapid)

Scarlet King Snake

“Red on yellow kill a fellow, red on black, venom lack”

A bite from the following snake is unlikely to result in …

(A) Ecchinocytosis

(B) Venom-induced thrombocytopenia

(C) Hypotension

(D) Lower motor neuron paralysis progressing to respiratory failure

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Answer: Copperhead (Crotalinae - pit viper) - toxicity is primarily hematologic abnormalities and coaguopathy, neurotoxicity can occur with any snake but is more common with elapids

Name 3 broad categories of toxicity that are associated with crotalinae envenomation

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- Coagulopathic - can be classified as FV and FX activators, activators of prothrombin, thrombin-like enzymes, anti-coagulant FIX/X binding proteins, activators of protein C, thrombin inhibitors, fibrinolytic enzymes, plasminogen activators

- Neurotoxins - presynaptic inhibition and progressive paralysis

- Myotoxins - myonecrosis and profound neuromuscular weakness

Name 2 enzymes that are commonly present in crotalinae venom and what effect they have

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- Crotalinae venom contains a mixture of water, proteins (enzymes) and peptides (exert organ toxicity).
- **Hyaluronidase** -> break down of connective tissues facilitating rapid spread of venom
- **Phospholipase A2**
    - -> cytotoxicity -> ecchinocytes, spherocytosis
    - -> anticoagulation through anti-Xa activity
- **Thromboxane** -> at least partially responsible for thrombocytopenia
- **Snake venom metalloproteinases (SMVPs)** -> platelet dysfunction and clinical hemmorhage
- **Proteases and endopeptidases** -> necrosis and coagulopathy

What is the mortality rate for crotalinae (pit viper) envenomation in dogs and cats in North America?

(A) <30%

(B) 30-60%

(C) 60-90%

(D) >90%

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Mortality rate for crotalinae envenomation is 1.8 - 24% in dogs and 6 - 18% in cats
Risk factors for death include age and increase time from envenomation to treatment

Patients are more likely to die from crotalinae envenomation if they are bit where?

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Head, eye(s) or tongue, predisposing to CNS envenomation or asphyxiation. Dogs that die from distal limb envenomation are assumed to have intra-arterial envenomation

List clinical signs and/or bloodwork abnormalities that may be seen in patients presenting with crotalinae envenomation

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- Pain, swelling, regional ecchymosis, one or two small puncture wounds.
- Compensatory or decompensatory shock
- Bites to tongue or mouth will swell rapidly and may cause upper airway obstruction
- Hyperglycemia and hypokalemia may be seen as a result of catecholamine surge
- Cardiac arrhythmias
- Hemolysis and/ or rhabdomyolysis may lead to pigmenturia
- Hemmorhage and/or hemolysis may lead to anemia
- Thrombocytopenia and/ or prolonged PT/PTT
- Hyperlactatemia due to tissue damage and hypoperfusion
- Widespread hemmorhage may lead to hematemesis, hematuria, melena, epistaxis, pulmonary infiltrates
- Neurotoxicity may lead to seizures, nystagmus or paralysis
- Hypoventilation if profound weakness or CNS involvement

True or false?

Traditional anti-venom is comprised of whole IgG molecules

True or false?

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TRUE

Table 141.1 Commonly available Crotalinae antivenom formulations.

Immunoglobulin type	Formulation	Supplied as	Venoms used in production	Approval status as of March 2018
IgG – equine Longest $T_{1/2}$ 150 kDa 2 venom-binding sites	Antivenom Crotalidae Polyvalent (ACP) Distributed by Boehringer Ingelheim Vetmedica	Lyophilized powder Slow reconstitution Room temperature storage	*Crotalus atrox*, *C. adamanteus*, *C. terrificus*, *Bothrops asper*	USDA approved for use in veterinary medicine
Fab – ovine Shortest $T_{1/2}$ 50 kDa 1 venom-binding site	CroFab® Distributed by Protherics	Lyophilized powder Fast reconstitution Room temperature storage	*Crotalus atrox*, *C. adamanteus*, *C. scutulatus*, *Agkistrodon piscovorus*	FDA approved for use in human medicine Off-label use in veterinary medicine
F(ab')2 – equine Longer $T_{1/2}$ than Fab, shorter than IgG 110 kDa 2 venom-binding sites	Venom Vet™ Produced by Instituto Biologico, Argentino S.A.I.C.	Liquid No reconstitution necessary Refrigeration necessary	*C. durissus*, *C. simus*, *Lachesis muta*, *Bothrops asper*, *B. alternatus*, *B. diporus*	USDA approved for use in dogs
F(ab')2 – equine Longer $T_{1/2}$ than Fab, shorter than IgG 110 kDa 2 venom-binding sites	Antivenom – *Bothrops asper* and *Crotalus durissus* Produced by Veteria Labs, S.A. de C.V.	Lyophilized powder Slow reconstitution Room temperature storage	*C. durissus*, *C. oreganus*, *C. o. helleri*, *C. adamanteus*, *C. scutulatus*, *C. atrox*, *C. horridus*, *Agkistrodon contortix*, *A. piscivorus*, *Bothrops asper*	Pending USDA approval for use in veterinary medicine Import permits required for experimental use

True or false?

Repeat bolusing or continuous rate infusion of anti-venom is not recommended

True or false?

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FALSE

Severe and protracted signs of envenomation (eg. neuromuscular collapse, profound hemolysis, and/or rhabdomyolysis) may require multiple repeat boluses of antivenom or as a CRI, eg. 1-2 vials over 6 hours continuously

Endpoints to stop include optimization of perfusion parameters, resolution of coagulopathy, resolution or significant improvement in echinocytosis and spherocytosis , lack of pigmenturia and/or progressive hemolysis, control of pain, and lack progressive swelling or tissue damage

True or false?

Dogs with a lower body weight typically require more anti-venom

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TRUE

True or false?

Dogs with an increased time from bite to presentation typically require more anti-venom

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True or false?

Diphenhydramine should be administered prophylactically to all patients receiving anti-venom

True or false?

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True or false?

Glucocorticoids should be administered prophylactically to all patients receiving anti-venom

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FALSE

Anaphylaxis is a rare but life-threatening complication from antivenom treatment given equine or ovine origins of antivenom. It is not necessary to perform intradermal testing or to administer prophylactic diphenhydramine or glucocorticoids, but should have epinephrine on-hand incase anaphylaxis occurs. Cats may be more likely to experience a reaction to antivenom infusion

A dog is currently hospitalized for monitoring after a rattlesnake bite. On his second day in the hospital he develops spherocytosis on his CBC, which was not present on his admission bloodwork. Which is the most appropriate treatment?

(A) Immunosuppresive doses of glucocorticoids

(B) Anti-venom

(C) No treatment is necessary

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ANSWER: B. Spherocytosis may be observed as late as 72 hours following initial envenomation, and treatment with antivenom should be prioritized over immune suppression.

Are the following treatments indicated in the treatment of pit viper envenomation?

1. Antibiotics
2. NSAIDs
3. FFP

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- Antibiotics: controversial; not routinely given in human medicine unless an infection develops. Some wounds may require treatment, likely due to secondary compartment syndrome and opportunistic infections.

- NSAIDs are not recommended given thee potential for AKI and GI ulceration.

- FFP is usually not indicated even if patient is experiencing hemmorhage. Coagulopathy is usually not due to factor deficiency, but rather a complex syndrome of factor inhibition, activation, platelet inhibition and endothelial dysfunction. Giving FFP provides extra substrate and may result in a procoagulant effect, unless all the venom is neutralized. This leads to excess fibrinolysis. pRBC transfusion may be necessary to treat anemia.

The most common cause of death from a bite from this snake is …

(A) Severe hemmorhage from coagulopathy

(B) Paralysis progressing to respiratory failure

(C) Seizures

(D) Bradycardia and resulting hypotension

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Elapid venoms are primarily neurotoxin, resulting in paralysis

How do elapids venoms cause paralysis?

How do elapids venoms cause paralysis?

- Neurmuscular junctionopathy, causing lower motor neuron paralysis. Many venoms contain both presynaptic and postsynaptic neurotoxins.

  - Phospholipase A2 - presynaptic neurotoxin, causes structural change to the nerve terminal and prevent release of acetylcholine. Presynaptic neurotoxins can become irreversibly bound and unresponsive to antivenom. Clinically it seems that it takes >24 hours for irreversible binding to occur.

  - Postsynaptic neurotoxins act as antagonists at acetylcholine receptors which reversibly bind, so there should be a better response to antivenom

What first aid advice should you give an owner after witnessing their dog being bitten by a coral snake?

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Recommend immediate presentation to veterinarian. The most common cause of death is respiratory paralysis, so you may instruct owners how to perform nose-to-snout ventilation en route if the patient is already collapsed. A pressure bandage may be placed over the bit site to prevent venom absorption, however this is not possible if the wound is on the head, neck or thorax.

A dog presents after potential contact with a North American Coral snake. The patient is asymptomatic and physical exam is unremarkable. What is your recommendation?

A dog presents after potential contact with a North American Coral snake. The patient is asymptomatic and physical exam is unremarkable. What is your recommendation?

- IV access
- Obtain PT, aPTT, PCV/ TP
- Check for hemolysis and biochem to evaluate CK
- urinalysis (to look for pigmenturia)
- monitoring for 36 hours

Match the correct spider with the appropriate clinical syndrome

- Loxoscelism? Lactrodectism?
- Black widow? Brown recluse?
- Neurotoxicity -> paralysis? Dermonecrosis?

Match the correct spider with the appropriate clinical syndrome

- Loxoscelism / Lactrodectism
- Brown recluse/ Black widow
- Dermonecrosis/ neurotoxicity -> flaccid paralysis

What are the most clinically relevant toxins found in the venom of brown recluse spiders?

What are the most clinically relevant toxins found in the venom of brown recluse spiders?

- Phospholipase and hyaluronidase

- Key components of the venom include phospholipase and hyaluronidase. The venom can trigger an intense inflammatory response and has direct hemolytic effects; however the bite itself is not painful and people are often unaware that they were bit. Most bites will cause minor erythema and edema and are self-limited. Cutaneous loxoscelism describes the development of skin necrosis and ulceration, usually taking 72 hours to become evident. A dry, necrosis eschar forms and detaches after 2-3 weeks, leaving ulcerated lesion that can take weeks to months to heal.

- Non-specific systemic signs of cutaneous loxoscelism may include fever and vomiting. Systemic loxoscelism develops uncommonly, and is associated with intravascular hemolytic anemia developing over 7-14 days. AKI occurs rarely.

Name 3 differential diagnoses for a brown recluse spider bite.

Name 3 differential diagnoses for a brown recluse spider bite.

- soft tissue infection
- pyoderma
- neoplasia
- toxic epidermal necrolysis
- erythema multiform
- purpura fulminans
- localized vasculitis.

What is the recommended treatment for brown recluse spider bites?

What is the recommended treatment for brown recluse spider bites?

- First aid for a brown recluse side bite includes elevation and immobilization of the affected limb, ice packing of the bite site and local wound care. Most bites are self-resolving without intervention. Cases of severe necrosis may require surgical management, but this is very uncommon. Glucocorticoids are occasionally used. The prognosis for recover is excellent; the bite may cause significant scaring.

What is the most clinically relevant toxin found in black widow spider venom?

What is the most clinically relevant toxin found in black widow spider venom?

- alpha-latrotoxin

- Lactrodectism describes bites from the Lactrodectus species, i.e. the widow group of spiders; are found worldwide. The venom of these spiders contains numbers toxins, with the most clinically relevant being alpha-latrotoxin. This toxin has a unique selective effect on nerve endings causing initial activation followed by depletion of neurotransmitters and subsequent flaccid paralysis.

- The bite itself is minimally painful, but within 5-60 minutes local pain develops with increasing intensity, and there may be local swelling and puncture marks. About 1/3 of human cases will also have systemic signs. Death is rare, usually occurring in young or old patients.

Table 143.1 Systemic signs reported in human patients with latrodectism.

Organ system	Abnormality
Cardiovascular	Bradycardia, tachycardia, arrhythmias, hypertension
Respiratory	Bronchial secretions, bronchoconstriction, pulmonary edema
Central nervous system	Psychoses, amnesia, confusion, insomnia, hallucinations, delirium
Peripheral nervous system	Pain, lacrimation, salivation, rhinitis, priapism, mydriasis, miosis
Skeletal and smooth muscle	Hypertonia, clonic contractions, fasciculations
Gastrointestinal	Nausea, vomiting, heartburn, hypersalivation, acute abdomen
Renal	Urine retention due to sphincter tone
	Nephritis
Hematology	Leukocytosis, neutrophilia, lymphopenia, eosinophilia, monocytosis, hemoconcentration

Which of the following is true regarding theraphosidae (Tarantula) envenomation in dogs?

(A) All reported canine cases have resulted in death

(B) Envenomation is unlikely to be clinically significant

(C) Symptoms are typically delayed >24 hours

(D) Effects in humans are more severe than in dogs

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(C) Symptoms are typically delayed >24 hours

(D) Effects in humans are more severe than in dogs

Theraphosidae spiders include tarantulas, bird-eating for whistling spiders. Envenomation by these spiders have minor effects in humans but may have fatal effects in animals. There are several cases of theraphosidae envenomation in dogs in Australia, all of which died, usually within the first few hours of being bitten. This is not reported in the USA.

List potential clinical signs of scorpion envenomation and appropriate treatment

List potential clinical signs of scorpion envenomation and appropriate treatment

- Pain at the bite site
- Paresthesia, numbness
- Agitation, anxiety
- SNS activation - tachycardia, hypertensior
- Pulmonary edema
- Hypotension, cariogenic shock
- Severe neuromuscular excitation
- Seizures, coma

Table 143.2 Classification and treatment of scorpion stings for human patients [13].

Clinical Grade	Clinical Effects	Potential Treatment
Grade 1	Local manifestations only	
	Pain	Analgesia
	Paresthesia	Local anesthesia
	Numbness	
Grade 2	Autonomic excitation	Antivenom
	Hypertension	Prazosin
	Agitation and anxiety	Oral benzodiazepines
Grade 3		Antivenom
	Pulmonary edema	Oxygen therapy +/− mechanical ventilation, vasodilators (e.g. prazosin)
	Hypotension & cardiogenic shock	Dobutamine, other inotropes
	Severe neuromuscular excitation	Benzodiazepine infusion
Grade 4	Multiorgan failure including coma, seizures and end organ damage due to hypotension	Antivenom
		Mechanical ventilation
		Inotropes
		Benzodiazepine infusion
		Supportive care

The immune respond to hymenoptera envenomation is mediated by _____.

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Answer: IgE

4 types of hypersenitivity reactions (traditionally)

1. Type 1 - immediate; IgE dependent

2. Type 2 - cytotoxic; IgG or IgM dependent

3. Type 3 - immune-complex mediated; IgG, IgM immune-complex dependent

4. Type 4 - delayed; T lymphocyte dependent

Traditionally - anaphylaxis was attributed to Type 1 Hypersensitivity reaction, and non-IgE mediated reactions were called anaphylactoid reactions. However, we know now that cytotoxic (eg. transfusion) and immune-complex reactions (eg. administration of IgG) can also cause anaphylaxis. So this system doesn't really work.

IgE mediated pathway — mast cells, basophils, histamine, prostaglandins, leukotrienes, serotonin, PAF

List potential clinical signs of anaphylaxis

List potential clinical signs of anaphylaxis

- IgE mediated and is characterized cardiovascular collapse, respiratory difficulty, cutaneous or gastrointestinal signs
- Massive release of histamine (from mast cells and basophils)
- Cutaneous signs: urticaria, erythema, angioedema, pruritus
- Respiratory signs: dyspnea, bronchospasm, stridor, cough from laryngeal and pharyngeal edema, increased mucous production, bronchospasm
- Circulatory compromise: hypotension, poor tissue perfusion, tachycardia or vagally-mediated bradycardia, increased vascular permeability
- GI signs: nausea, vomiting, diarrhea, hematochezia
- Liver: hepatic venous congestion and portal hypertension
- Clinical signs of anaphylaxis should occur within 15-30 minutes, and time of onset is directly proportional to the severity of the signs

List potential complications from a delayed hypersensitivity reaction to hymenoptera envenomation

List potential complications from a delayed hypersensitivity reaction to hymenoptera envenomation

- Uncommon but can occur within days to weeks
- Results from tissue deposition of antigen-antibody complexes
- Resultant inflammatory cascade leads to complement binding and subsequent formation of anaphylatoxin, causing mast cell degranulation and histamine release, leading to vasculitis, polyarthritis, glomerulonephritis, and myocardial lesions

Outline appropriate treatment of anaphylaxis

Outline appropriate treatment of anaphylaxis

- Immediate administration as an IV bolus 0.01 mg/ kg followed by a CRI 0.05 ug/ kg/min
- Secure airway if upper airway obstruction is present
- Aggressive fluid resuscitation
- Glucocorticoid use is controversial
- Antihistamines to relieve symptoms of urticaria and pruitis
- Bronchodilators (albuterol, aminophylline)
- Vasopressors if refractory hypotension