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Hymenoptera Envenomation

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Apoidea

The family Apoidea includes the social honey bees, bumble bees, and solitary bees. These insects are social and herbivorous, feeding off flower pollen and nectar. They build their nests (hives) in hollow trees or other cavities. Nests of bumble bees contain 100–200 insects and are typically not involved in mass envenomations whereas honey bee (*Apis mellifera*) hives often contain thousands of workers, with 40 000 workers in some managed colonies [1].

Africanized honey bees (AHB) are a tropical variety of honey bee that was imported from Africa to Brazil in 1956 to improve honey production [2]. This variety of bee, known for its aggressive temperament leading to mass envenomation, escaped and replaced the local honey bee variety in Brazil, reaching the United States by 1990 [3]. As of 2011, AHBs have spread to 10 US states although attacks have not been noted in all of these states [4]. AHBs are quicker to attack and will chase their victims up to 0.6 miles, as compared to European honey bees which will follow for up to 500 yards. AHBs also tend to establish a larger number of colonies in less protected locations within a particular geographic area, making them more easily disturbed [5].

Bees can only sting once, as their barbed stinger remains in the victim's skin following envenomation. After a sting, the stinger and venom sac are pulled out of the bee's abdomen, resulting in the insect's death shortly thereafter [6,7].

Vespoidea

The family Vespoidea includes the wasps, hornets, and yellowjackets. These insects are predacious carnivores, feeding on other insects and sweet substances such as

sap and nectar, that frequently forage near open food containers and garbage. Stings typically occur via a single vespid and most commonly occur in the late summer and early fall when hungry yellowjackets are attracted to the smell of human food prepared outdoors [6]. Mass envenomation may occur when a colony is disturbed. Hornets and wasps typically inhabit trees and shrubs, while yellowjackets are frequently ground dwellers. Compared to the Apoidea, vespids tend to be more aggressive and possess smooth stingers which allow them to deliver multiple stings [7,8].

Formicidea

The family Formicidea contains the ants. Those medically relevant include the black and red imported fire ant (*Solenopsis invicta* and *S. richteria*). Both are native to South America and entered the United States in the 1900s [9], where they formed hybrids with native species. The black imported fire ants are mostly confined to Alabama and Mississippi but the red imported fire ants and hybrids are highly adaptive and have spread to 12 southern states. Red fire ant hybrids appear to be cold resistant and can overwinter, allowing for northward migration into areas with a cooler climate [10].

Fire ants form mounds which can interfere with farming. They may attack livestock and other native species and increasingly are reported to attack pets and debilitated humans [11]. Imported fire ants are omnivorous, stinging and killing invertebrates as their primary food source. Fire ants can quickly swarm a victim, using pheromone cues to sting simultaneously. The fire ant initially bites its prey with its prominent mandibles and, once anchored, tucks its abdomen to sting with a non-barbed stinger. The ant then remains attached by its mandibles, removes its stinger, rotates its body, and stings again.

This is repeated 6–7 times in a circular pattern, with venom slowly injected over 20–30 seconds. This results in a slower onset and less painful sting than those delivered by bees or vespids [12,13].

Venom

Bee venom is a complex mixture of proteins and biologically active peptides. Mellitin, the major component and the main cause of pain following a sting, is a detergent, which alters cell membrane integrity. Mellitin works synergistically with the primary allergen of venom, phospholipase A₂, to cause red blood cell, platelet, leukocyte, and vascular endothelial cell lysis [1,14], and is suspected to cause myelinolysis of the spinal cord [13,15]. Other venom components include mast cell degranulating factor, which causes histamine and vasoactive amine release from mast cells, and hyaluronidase, which disrupts collagen, allowing venom to spread to adjacent tissues. Bee venom also contains vasoactive amines such as histamine, dopamine, and norepinephrine, and apamin, a neurotoxin that acts on the spinal cord [13].

Wasp venoms are more heterogeneous but most contain three major allergenic peptides as well as vasoactive amines (serotonin, histamine, tyramine, catecholamines), wasp kinins, and acetylcholine. The vasoactive substances are responsible for the intense pain of wasp stings. Antigen 5 is the most allergenic component but its activity is poorly understood. Other venom components include phospholipase A and B, which cleave lipid bilayers, and hyaluronidase. Vespid venom does not contain mellitin [16].

Unlike the venom of other Hymenoptera, which are composed primarily of proteins in an aqueous solution, fire ant venom is composed of 95% water-insoluble alkaloids. These alkaloids are primarily piperidines which have cytotoxic, hemolytic, antibacterial, and insecticidal properties [13]. They do not produce an IgE-mediated reaction, but instead produce sterile pustules secondary to tissue inflammation which are almost pathognomonic for fire ant stings [17].

Lethal Dose

Stinging insects are not able to meter their venoms like some venomous snakes and deliver a relatively standard volume of venom per sting. The European honey bee is thought to inject 147 µg of venom per sting, with most wasps injecting about 17 µg of venom per sting [17]. Africanized honey bees likely inject a slightly smaller volume of venom per sting than their European counterparts. The lethal dose for bee, wasp

or hornet envenomation is approximately 500 stings per adult human [1,8,18] and is estimated to be 20 stings/kg in most mammals [1,19]. Each fire ant sting can deliver 0.11 µL of venom, with up to 20 consecutive stings being delivered before venom stores are depleted. Severe systemic reactions have been reported following 50–100 fire ant stings in humans. While fatal envenomation can occur in animals, the lethal dose is unknown [20].

Clinical Manifestations of Envenomation

Hymenoptera envenomation may result in local tissue reactions, immune-mediated responses or, rarely, venom systemic toxic effects. A local reaction, characterized by edema, erythema, and pain at the site of envenomation, occurs following all Hymenoptera envenomation as a result of the vasoactive properties of the venom. This is typically self-limiting and generally resolves within 24 hours [13].

Immune-Mediated Response

Immune-mediated response to envenomation can be divided into three subtypes: regional reaction, systemic anaphylaxis, and delayed hypersensitivity reaction. Regional reactions are thought to be IgE mediated and involve the area immediately surrounding the site of the sting. Regional reactions can be extensive and may lead to erythema and edema encompassing an entire extremity. This may not be apparent for up to 24 hours following a sting and will typically peak in severity within 48 hours, although signs may not resolve for several days and may be confused with cellulitis [13,21].

Systemic anaphylaxis, though rare, is the most life-threatening reaction to Hymenoptera envenomation (see Chapter 146). It is mediated by IgE and is characterized by all or a combination of clinical signs related to cardiovascular collapse, respiratory difficulty, or cutaneous or gastrointestinal signs. Clinical signs are due to massive release of a variety of chemical mediators, primarily histamine, from mast cells and basophils. Cutaneous signs include urticaria, erythema, angioedema, and pruritus. Respiratory signs include dyspnea, bronchospasm, stridor, and cough as a result of laryngeal and pharyngeal edema, increased mucus production, and bronchoconstriction. Circulatory compromise is characterized by hypotension and signs of poor tissue perfusion (pale mucous membranes, prolonged capillary refill time, poor pulse quality, and dull mentation) due to vasodilation and increased vascular permeability. Tachycardia or, less commonly, vagally mediated bradycardia may be seen. Arrhythmias,

myocardial ischemia, and cardiac arrest may also occur. Gastrointestinal signs may include nausea, vomiting, and diarrhea or hematochezia. Other clinical signs which may occur include weakness, syncope, lacrimation, conjunctival hyperemia, and seizures.

Clinical signs of anaphylaxis typically occur within 15 minutes of the insult and are unlikely to occur if no signs are noted within 30 minutes. The time to onset of signs is directly proportional to the severity of the signs. Depending on the severity and manifestation of anaphylaxis, death can occur within minutes [22].

Delayed hypersensitivity reactions are uncommon but can occur within days to weeks of envenomation, resulting from tissue deposition of antigen-antibody complexes. The resultant inflammatory cascade leads to complement binding and subsequent formation of anaphylatoxin, causing mast cell degranulation and histamine release which results in damage to the basement membrane. This may result in vasculitis, polyarthrititis, glomerulonephritis, and myocardial lesions [13,22].

Systemic Toxic Reactions

Systemic toxic reactions occur due to the direct effects of venom and are related to the total volume of venom injected. Clinical signs can include fever, depression, ataxia, seizures, pigmenturia, hypotension, and melena or hematochezia [23]. Secondary immune-mediated hemolytic anemia and thrombocytopenia have been reported in dogs following massive bee and vespid envenomation [24–31] (see Chapter 66). Mellitin and phospholipase A2 may cause rhabdomyolysis, leading to myoglobinemia, myoglobinuria and potentially a pigment nephropathy. Ataxia, transient facial nerve paralysis, seizure, and other neurological dysfunction secondary to the effects of mellitin and apamin have been reported in dogs [13,25]. Acute respiratory distress syndrome (ARDS) may occur following massive envenomation [24,26,32]. One case report describes a dog which was mechanically ventilated for suspected ARDS secondary to massive bee envenomation; this dog ultimately recovered to discharge [33]. Coagulopathy and disseminated intravascular coagulation are also commonly reported, likely due to hepatocellular injury and release of tissue thromboplastin and endothelial cell disruption [26,34] (see Chapter 70).

Only one published case report describes massive envenomation of two dogs by fire ants in Australia. Both dogs developed acute kidney injury (see Chapter 94). One dog died, and necropsy revealed evidence of mesenteric and myocardial hemorrhage as well as renal tubular necrosis [35].

Diagnosis

Definitive diagnosis may be challenging if the incident was not witnessed, but the circumstances may raise a clinical suspicion for Hymenoptera envenomation. Depending on the type of reaction, there may be few biochemical or radiographic changes noted. Local and regional reactions are diagnosed on physical examination. Anaphylaxis is often a clinical diagnosis, but elevations in ALT and ultrasound evidence of gall bladder wall edema have been associated with anaphylaxis in dogs [36–38]. Animals presenting with delayed or toxic reactions may show evidence of hepatopathy (elevated ALT, AST, ALP, GGT, bilirubin), azotemia secondary to acute kidney injury, urinary casts, evidence of rhabdomyolysis (elevated CK, myoglobinemia, myoglobinuria), evidence of immune-mediated hemolytic anemia or thrombocytopenia (spherocytosis, anemia, thrombocytopenia, hemoglobinemia, hemoglobinuria), or coagulopathy (prolonged PT/PTT, thrombocytopenia, and elevated D-dimers). Complete blood count may also reveal an inflammatory leukogram [13].

Treatment

Local or mild regional reactions often do not require treatment but application of ice or cool compresses, and oral or injectable antihistamines (1–2 mg/kg diphenhydramine IM, PO) may be helpful [14]. Sarna lotion (camphor and menthol) can be applied topically for fire ant stings. Topical use of meat tenderizer (papain) or aluminum sulfate has not been demonstrated to be effective. Animals with multiple stings or with severe regional reactions should be hospitalized to monitor for the development of systemic toxic reactions. Human recommendations are to hospitalize patients for 24 hours following massive envenomation of >50 stings [39].

Hypotension should be treated aggressively with intravenous fluid therapy see (Chapter 167). Maintenance of normotension and adequate tissue perfusion is of utmost importance. Appropriate analgesia (see Chapter 193) should be provided and while broad-spectrum antibiotics are not typically required, they should be administered if secondary infection develops [13,22,24].

Treatment of Systemic Anaphylaxis

Anaphylaxis is a medical emergency and survival is dependent on immediate patient assessment and stabilization (see Chapter 146). Immediate administration of epinephrine (Table 145.1) given as an IV bolus is indicated, followed by CRI of epinephrine titrated to

Table 145.1 Treatment of systemic anaphylaxis [22].

Medication	Dog dosage	Cat dosage
Epinephrine	0.01 mg/kg (1 mg/mL solution) IM/IV q5–15 min Max dose: 0.3 mg < 40 kg, 0.5 mg > 50 kg CRI: 0.05 µg/kg/min if shock is present	0.01 mg/kg (1 mg/mL solution) IM/IV q5–15 min CRI: 0.05 µg/kg/min if shock is present
Isotonic crystalloid	90 mL/kg (in aliquots, to effect)	60 mL/kg (in aliquots, to effect)
Colloids (Hetastarch)	5 mL/kg bolus, up to 20 mL/kg	5 mL/kg bolus, up to 20 mL/kg
Methylprednisolone sodium succinate	30 mg/kg IV	30 mg/kg IV
Dexamethasone sodium phosphate	1–4 mg/kg IV	1–4 mg/kg IV
Prednisone sodium succinate	10–25 mg/kg IV	10–25 mg/kg IV
Diphenhydramine	1–4 mg/kg IM or PO q8–12h 0.5–1 mg/kg IV slowly (not >50 mg total)	0.5–2 mg/kg IM or PO q8–12h
Ranitidine	0.5–2 mg/kg IV, PO or SC Give IV slowly over 10 min	0.5–2 mg/kg IV, PO or SC Give IV slowly over 10 min
Albuterol	0.5 mL of 0.5% solution in 4 mL isotonic saline by nebulizer q6h, 90 µg/actuation (1–2 puffs) by metered dose q15min for 3 doses	0.5 mL of 0.5% solution in 4 mL isotonic saline by nebulizer q6h, 90 µg/actuation (1–2 puffs) by metered dose q15min for 3 doses
Aminophylline	5–10 mg/kg IM or slowly IV	5–10 mg/kg IM or slowly IV
Vasopressin	CRI: 0.5–1.25 mU/kg/min	CRI: 0.5–1.25 mU/kg/min
Norepinephrine	CRI: 0.1–1 µg/kg/min	CRI: 0.1–1 µg/kg/min
Dopamine	CRI: 2.5–10 µg/kg/min	CRI: 2.5–10 µg/kg/min
Glucagon	1–2 mg/kg followed by CRI: 5–15 mg/min	1–2 mg/kg followed by CRI: 5–15 mg/min
Atropine	0.02–0.04 mg/kg IV	0.02–0.04 mg/kg IV
Ipratropium	18 µg/actuation, via inhalation	18 µg/actuation, via inhalation

CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

clinical response if shock is present. The airway should be secured and the patient intubated if necessary, and supplemental oxygen should be provided.

Aggressive fluid resuscitation is recommended in hypotensive patients. Bolus IV infusion of an isotonic crystalloid solution should be administered at resuscitative volumes (90 mL/kg in dogs and 60 mL/kg in cats, given in aliquots to effect). Colloids may be beneficial in providing a more sustained hemodynamic response and can be administered in bolus form.

Glucocorticoid use is controversial and a Cochrane review showed no benefit of administration during systemic anaphylaxis [40]; however, glucocorticoid use may reduce the severity of inflammation in late stages of anaphylaxis. Antihistamines (H1 and H2 antagonists) may

be administered to relieve symptoms, particularly urticaria and pruritus, and they may decrease gastric acid secretion.

Bronchodilators may be another useful adjunctive therapy. Albuterol acts to relieve bronchospasm by relaxing bronchial smooth muscle [41]. Aminophylline, in addition to smooth muscle relaxation, also increases endogenous epinephrine release and decreases histamine release via phosphodiesterase inhibition [42].

Refractory hypotension may require treatment with vasopressors such as norepinephrine, vasopressin or dopamine. Refractory bronchospasm can be treated with glucagon or inhaled ipratropium. Persistent bradycardia or previous administration of beta-blockers may necessitate treatment with an anticholinergic [22].

Treatment of Toxic and Delayed Reactions

Massive envenomation requires aggressive, rapid stabilization with IV fluids to improve perfusion as well as provision of analgesia. Depending on the clinical manifestation, ancillary therapies may include antihistamine and corticosteroid administration to reduce upper airway edema and pruritus, plasma transfusion to treat DIC

or coagulopathy, hemodialysis for severe or oligoanuric acute kidney injury (see Chapter 94), and oxygen support or mechanical ventilation for acute lung injury/acute respiratory distress syndrome (see Chapter 181). Epinephrine should be considered if there is suspicion of an anaphylactic component to the reaction. Broad-spectrum antibiotic therapy should be considered, particularly for fire ant massive envenomation [13] (see Chapter 200).

References

- Vetter RS, Camazine S. Mass envenomation by honey bees and wasps. *West J Med* 1999;170(4):223–227.
- Gonsalves LS. The introduction of the African Bees (*Apis mellifera adasonii*) into Brazil and some comments on their spread in South America. *Am Bee J* 1974;114:414–419.
- Rowell MS, Bradley L, Cole C. The range expansion of the Africanized honey bee in Texas. *Am Bee J* 1993;133:84–85.
- United States Department of Agriculture. Agriculture Research Service: Spread of Africanized Honey Bees by Year, updated March, 2011. www.ars.usda.gov/Research/docs.htm?docid=11059&page=6 (accessed 8 February 2018).
- Kim KT, Oguro J. Update on the status of Africanized honey bees in the Western States. *West J Med* 1999;170:220–222.
- Goddard J. *Physicians Guide to Arthropods of Medical Importance*, 3rd edn. WB Saunders, Philadelphia, 2000.
- Winston ML. Form and function: honey bee anatomy. In: *The Biology of the Honey Bee*. Harvard University Press, Cambridge, 1987, pp. 13–45.
- Smallheer BA. Bee and wasp stings: reactions and anaphylaxis. *Crit Care Nurs Clin North Am* 2013;25(2):151–164.
- Logren CS, Banks WS, Glancey BM. Biology and control of imported fire ants. *Ann Rev Entomol* 1975;20:1–30.
- Kemp SF, deShazo RD, Mofitt JE, et al. Expanding habitat of the imported fire ant (*Solenopsis invicta*): a public health concern. *J Allergy Immunol* 2000;105:683–691.
- deShazo RD, Kemp SF, deShazo MD, Goddard J. Fire ant attacks on patients in nursing homes: an increasing problem. *Am J Med* 2004;116(12):843–846.
- Stafford CT. Hypersensitivity to fire ant venom. *Ann Allergy Asthma Immunol* 1996;77:87–95.
- Fitzgerald KT, Flood AA. Hymenoptera stings. *Clin Techn Small Anim Pract* 2006;21(4):194–204.
- Peters LJ, Kovacic JP. Histamine: metabolism, physiology, and pathophysiology with applications in veterinary medicine. *J Vet Emerg Crit Care* 2009;19(4):311–328.
- Schmidt JO, Blum MS, Overall WL. Comparative enzymology of venoms from stinging Hymenoptera. *Toxicon* 1986;24(9):907–921.
- Bachman DS, Paulson MD, Jerry R, Mendell MD. Acute inflammatory polyradiculoneuropathy following Hymenoptera stings. *JAMA* 1982;247(10):1443–1445.
- Nakajima T. Pharmacological biochemistry of vespid venoms. In: *Venoms of the Hymenoptera: Biochemical, Pharmacological and Behavioral Aspects* (ed. Piek T). Academic Press, Orlando, 1986, pp. 309–327.
- Vetter RS, Visscher PK. Bites and stings of medically important venomous arthropods. *Int J Dermatol* 1998;37:481–496.
- Franca FO, Benvenuti LA, Fan HW, et al. Severe and fatal mass attacks by “killer bees” in Brazil: clinicopathological studies with measurement of serum venom concentrations. *QJ Med* 1994;87:269–282.
- Brand JM, Blum MS, Fales HM, et al. Fire ant venoms: comparative analysis of alkaloidal components. *Toxicon* 1972;10:259–271.
- Reisman RE. Current concepts: insect stings. *N Engl J Med* 1994;331(8):523–527.
- Shmuel DL, Cortes Y. Anaphylaxis in dogs and cats. *J Vet Emerg Crit Care* 2013;23(4):377–394.
- Riches KJ, Gillis D, James RA. An autopsy approach to bee sting related deaths. *Pathology* 2002;34:257–262.
- Cowell AK, Cowell RL. Management of bee and other Hymenoptera stings. In: *Kirk's Current Veterinary Therapy XII* (ed. Bonagura JD). WB Saunders, Philadelphia, 1995, pp. 226–228.
- Waddell LS, Drobotz KJ. Massive envenomation by *Vespula* spp. in two dogs. *J Vet Emerg Crit Care* 1999;9(2):67–71.
- Wysoke JM, van den Berg PB, Marshall C. Bee sting-induced haemolysis, spherocytosis and neural dysfunction in three dogs. *J S Afr Vet Assoc* 1990;61(1):29–32.
- Cowell AK, Cowell RL, Tyler RD, et al. Severe systemic reactions to Hymenoptera stings in three dogs. *J Am Vet Med Assoc* 1991;198(6):1014–1016.
- Noble SJ, Armstrong PJ. Bee sting resulting in secondary immune-mediated hemolytic anemia in two dogs. *J Am Vet Med Assoc* 1999;214(7):1026–1027.

- 29 Nakamura RK, Fenty RK, Bianco D. Presumptive immune-mediated thrombocytopenia secondary to massive Africanized bee envenomation in a dog. *J Vet Emerg Crit Care* 2013;23(6):652–656.
- 30 Grisotto LSD, Mendes E, Castro I, et al. Mechanisms of bee venom-induced acute renal failure. *Toxicon* 2006;48:44–54.
- 31 Oliveira EC, Pedroso PMO, Meirelles AE, et al. Pathologic findings in dogs after multiple Africanized bee stings. *Toxicon* 2007;49:1214–1218.
- 32 Mughal MN, Abbas G, Saqib M, Muhammad G. Massive attack by honeybees in a German Shepherd dog: description of a fatal case and review of the literature. *J Venom Anim Toxins Trop Dis* 2014;20:55.
- 33 Walker W, Tidwell AS, Rozanski EA, et al. Imaging diagnosis: acute lung injury following massive bee envenomation in a dog. *Vet Radiol* 2005;46(4):300–303.
- 34 Figuera RA, Mello de Souza T, Lombardo de Barros CS. Bee sting as a cause of death in dogs. *Ciência Rural* 2007;37(2):590–593.
- 35 Abraham LA, Hinkley CJ, Tatarczuch L, et al. Acute renal failure following Bull Ant mass envenomation in two dogs. *Aust Vet J* 2004;82(1,2):43–47.
- 36 Peters GA, Karnes WE, Bastron JA. Near-fatal and fatal anaphylactic reactions to insect sting. *Ann Allergy* 1978;41:268–273.
- 37 Quantz JE, Miles MS, Reed AL, et al. Elevation of alanine transaminase and gallbladder wall abnormalities as biomarkers of anaphylaxis in canine hypersensitivity patients. *J Vet Emerg Crit Care* 2009;19(6):536–544.
- 38 Thomas E, Mandell DC, Wadell LS. Survival after anaphylaxis induced by a bumblebee sting in a dog. *J Am Anim Hosp Assoc* 2013;49(3):210–215.
- 39 Kolecki PK. Delayed toxic reaction following massive bee envenomation. *Ann Emerg Med* 1999;33(1):114–116.
- 40 Choo KJ, Simmons FE, Sheikh A. Glucocorticosteroids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2010;65(10):1205–1211.
- 41 Simons FE. Anaphylaxis. *J Allergy Clin Immunol* 2010;125(2 suppl 2):S161–181.
- 42 Plumb DC. *Plumb's Veterinary Drug Handbook*, 6th edn. Blackwell Publishing, Ames, 2008.