Management of Snake Envenomation in Taiwan

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Abstract

There are six venomous snakes of medical importance in Taiwan: three crotalids, *Trimeresurus (Viridovipera) stejnegeri*, *Protobothrops mucrosquamatus*, and *Deinagkistrodon acutus*; one viperid, *Daboia russelli siamensis*; and two elapids, *Naja atra* and *Bungarus multicinctus*. In the prehospital settings, there is no role for incision and suction, electrotherapy, and cryotherapy for snakebite wounds. Routine use of a constriction band or pressure immobilization device is not indicated. The Taiwan government produces four types of equine-derived antivenoms to treat the above-noted snakebites, namely, bivalent antivenom for *T. stejnegeri* and *P. mucrosquamatus*, bivalent antivenom for *N. atra* and *B. multicinctus*, and two monovalent antivenoms for *D. acutus* and *D. r. siamensis*, respectively. These antivenoms are $F(ab')_2$ fragment in the lyophilized form containing 2,000 units per vial (or at least 1,000 Tanaka units). The Taiwan Poison Control Center formulated a flowchart for the management of six major venomous snakebites based on animal studies, clinical observation, and expert opinion in 1999. The recommended dosage of relevant antivenoms is 1–2 vials for *T. stejnegeri* snakebites, 2–4 vials for *P. mucrosquamatus*, 2–4 vials for *D. acutus*, 2–4 vials for *D. r. siamensis*, 6–10 vials for *N. atra*, and 2–4 vials for *B. multicinctus*. The use of antibiotics is suggested when secondary wound infection has developed, whereas surgical indications include wound necrosis, abscess formation, distal limb gangrenous change, necrotizing fasciitis, or, in rare cases, compartment syndrome. Further studies on the severity assessment (e.g., severity score), risk factors for the development of severe disease, optimal dosing of antivenom, effect of prophylactic antibiotics, and timing of surgery in cases of venomous snakebites in Taiwan are warranted.

Introduction

Taiwan is an island that lies at the junction of the tropical and subtropical zone and is heavily forested with dense undergrowth, mountainous and hilly terrains, and seasons of high rainfall. Taiwan's terrains and warm climate provide a highly suitable habitat for snakes. There are 61 (52) snake species that inhabit the island, of which 29 (22) are venomous, including 13 (7) sea snakes and 16 (15) land snakes (Hsiang et al. 2009; Tu 2008). These numbers are variable (shown in parentheses) according to different reports because some of the snake species are extremely rare or may even be exotic. Among the indigenous venomous species, only six land snakes are considered medically important. They are *Trimeresurus (Viridovipera) stejnegeri*, *Protobothrops mucrosquamatus*, *Deinagkistrodon acutus*, *Daboia russelli siamensis*, *Naja atra*, and *Bungarus multicinctus*. The former three belong to the subfamily Crotalinae; *D. r. siamensis* belongs to Viperinae, whereas the remaining two belong to the family Elapidae. The managements of snake

envenomations include snake identification, first aids, prompt transportation to healthcare facilities, timely administration of relevant antivenom, antibiotic therapy, and/or surgical interventions whenever indicated. The Taiwan government developed endemic antivenoms quite early. In the 1980s, the Vaccine Center further modified the manufacturing processes to improve the quality and speed of production of antivenoms (Huang et al. 1985; Huang et al. 1986; Liau and Huang 1997; Liau et al. 1982). In 1995, Taiwan established a National Health Insurance system, and in 1999, the Taiwan Poison Control Center (PCC-Taiwan) formulated a flowchart on the management of the six medically important venomous snakebites (Hung et al. 1999). The good quality of antivenoms, easy accessibility to modern medical care, and standardization of management protocol have jointly improved the outcome of snake envenomations in Taiwan. The case-fatality rate declined from 24 deaths per year before 1940 to 1 death out of 286 cases during 1993–2000 (Hung 2004; To 1941) and 3 deaths out of 3,862 cases during 2002–2005 (Liu et al. 2009).

Brief Review of the Epidemiology of Snake Envenomation in Taiwan

In Taiwan, systemic evaluations of snakebites started during the Japanese colonial period (1895–1945). Snakebite was once a compulsorily reported disease. Dr. To analyzed the statistics archived by the government in Taiwan during 1904–1938 and estimated that on average there were 361.3 cases of snakebite with 24 deaths per year (To 1941). After World War II (1945), the recording of snakebite statistics by the government was discontinued. Sawai et al. reinvestigated the epidemiology of snakebites, reporting a total of 891 cases and 19 deaths in the 1960s (Sawai and Tseng 1969). In a recent study utilizing the National Health Insurance claims database, 3,862 snakebite cases with 3 deaths were identified during 2002–2005 (Liu et al. 2009). Overall, *T. stejnegeri* is the most common offending snake among the six major venomous snakes, followed by *P. mucrosquamatus*, *B. multicinctus*, *N. atra*, *D. acutus*, and *D. r. siamensis*. Snakebites generally occur during April to October, the warm and rainy seasons in Taiwan. Kuo and Wu identified another peak of incidence in November, a winter month, in the southern part of Taiwan, which may be related to the fact that this is generally the last month in a year to harvest in that tropical region. There is also a clear preponderance of males among snakebite victims; however, the mean age of snakebite patients is increasing. In recent reports, the mean age of snakebite victims was more than 40 years, while the median age was around 50 years (Chang et al. 2007; Chen et al. 2000b; Liao et al. 2000; Liu et al. 2009; Shih et al. 2006). The increase in age of snakebite victims probably heralds the aging of population and the shrinkage in agriculture manpower in Taiwan. Snake envenomation in the elderly (Warrell 2010) may lead to higher medical expenses, which demands further investigation.

Characteristics of Six Major Venomous Snakes and Snakebites

Except for *T. stejnegeri*, five of the six medically important venomous snakes are endangered in Taiwan and are under protection according to the Wildlife Conservation Act. All six snakes have distinct biological features (Fig. 2.1); thus, capturing or killing them for identification is not necessary. Nevertheless, it can be helpful

Fig. 2.1 Features of six medically important venomous snakes in Taiwan (Pictures were provided and used with the permission from Mr. Chih-Ming Lai)

Viperidae: *Ovophis monticola makazayazaya*

Viperidae: *Trimeresurus gracilis*

Elapidae: *Sinomicrurus hatori*

Elapidae: *Sinomicrurus sauteri*

Elapidae: *Sinomicrurus macclellandi swinhoei*

Colubridae: *Rhabdophis tigrinus formosanus*

Fig. 2.2 (continued)

in the management of snakebites if the victim or their companions remember the color pattern of the offending snake or if the snake can be identified by medical staff in case of captured snake. For comparative purposes, the features of 10 less venomous land snakes are also shown here (Fig. 2.2).

Fig. 2.2 Ten less venomous land snakes are shown with family and scientific names (Pictures are provided and used with the permission from Mr. Chih-Ming Lai)

Snake envenomations can result in various categories of toxic effects, including coagulopathy, neurotoxicity, myonecrosis, renal injury, cardiotoxicity, and severe local tissue damage at bitten site. Any single species of snake may show activity in one or more of the above-noted categories (White 2005). A summary of the distribution (Hsiang et al. 2009; Lin et al. 1990; Tu 2008), venoms, and clinical manifestations of the six medically important venomous snakes and related bites in Taiwan is presented in this chapter.

Trimeresurus (Viridovipera) stejnegeri

(a) **Distribution**

T. stejnegeri is found in India, Nepal, Myanmar, Thailand, Vietnam, Laos, and southern China. In Taiwan, it occurs more commonly at lower altitudes of wooded, shrub, and mountainous areas.

(b) **Venom**

Ouyang had demonstrated that the venoms of *T. stejnegeri* and *D. acutus* had anticoagulant effect in low concentration and procoagulant in high concentration, though this effect was less prominent in the former (Ouyang 1957). Venom of *T. stejnegeri* contains several proteins and peptides including thrombin-like enzyme (TLE), prothrombin activation inhibitor (acidic phospholipase A), fibrinogenases, platelet aggregation inhibitor, platelet aggregation inducer, and hemorrhagins (e.g., metalloproteinases), (Huang et al. 1984; Ouyang and Huang 1983a; Ouyang et al. 1982a). TLE acts on fibrinogen similar to thrombin, producing the procoagulant effect. On the other hand, TLE differs from thrombin: it digests fibrin and the fibrin formed by this enzyme is more susceptible to plasmin degradation than fibrin formed by thrombin. TLE also does not activate coagulation factor VIII and is not inhibited by heparin (Ouyang and Yang 1974). Prothrombin activation inhibitor interferes with prothrombin and its activation factors through reversible binding to these factors (Ouyang and Yang 1975). Fibrinogenases cause fibrinogenolysis and fibrinolysis. The degradation products of fibrinogen might further polymerize with fibrin and prolong the reaction time of thrombin to fibrinogen.

A potent platelet aggregation inhibitor and an inducer both were isolated from the *T. stejnegeri* venom. The inhibitor, with 5′-nucleotidase, which cleaves adenosine diphosphate (ADP), inhibits ADP- or collagen-induced platelet aggregation without platelet lysis. It also inhibits the thrombin-induced clot stabilization (Huang and Ouyang 1984) and causes indirect hemolysis in the presence of phosphatidylcholine (Ouyang and Huang 1983b). In experimental models, the crude venom elicits platelet aggregation in low concentration (<100 μg/ml); however, this action declines in higher concentrations (Ouyang and Huang 1983a).

Hemorrhagins, α-fibrinogenase, and hemorrhagin II are metalloproteinases and may be the key factor causing systemic injury, local damage, hemorrhage, edema, and necrosis (Markland and Swenson 2013). Their relative hemorrhagic activity compared to crude venom was 1:2:8 (Huang et al. 1984). Crude venom contains phospholipase A_2, which may potentiate the hemorrhagic activity of hemorrhagins. The actions of hemorrhagins in *T. stejnegeri* envenomation might be reverse by relevant antivenom (Huang et al. 1984).

(c) **Clinical manifestations**

Clinical manifestations and treatment of *T. stejnegeri* and *P. mucrosquamatus* envenomations are quite similar although they are biologically distinct. Chen et al. studied 50 cases of *T. stejnegeri* bites and reported the following symptoms and signs in decreasing frequency: local pain (100 %), inflammation (100 %), bruising (51 %), transient bleeding from fang marks (22 %), mild thrombocytopenia (10 %), cellulitis (6 %), renal dysfunction (4 %), rhabdomyolysis (2 %), and

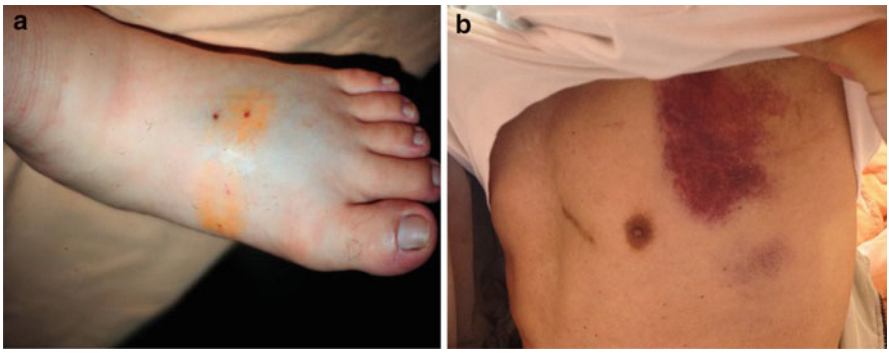

Fig. 2.3 (**a**) Patient was bitten by *T. stejnegeri* on the foot. (**b**) Patient was bitten by *T. stejnegeri* on the left hand and distant ecchymosis developed over the chest wall 1 day later

compartment syndrome (2 %) (Chen et al. 2009). Occasionally, there was bruising distant away from the bitten area (Fig. 2.3); however, significant wound bleeding or bleeding from the vital organs was not observed.

Protobothrops mucrosquamatus

(a) **Distribution**

P. mucrosquamatus is widely distributed in northeastern India, Bangladesh, Myanmar, southern China, and Taiwan.

(b) **Venom**

The venom of *P. mucrosquamatus* contains prothrombin activation inhibitor (basic phospholipase A), fibrinogenases, platelet aggregation inducer, and platelet aggregation inhibitors (Ouyang and Teng 1978; Ouyang et al. 1982b). The anticoagulant effect of prothrombin activation inhibitor, which could be reversed by the antivenom, may be due to both enzymatic and strong binding activities, inhibiting prothrombin and factor X through the inactivation of the procoagulant activity of phospholipids. Fibrinogenases isolated from *P. mucrosquamatus* venom, similar to that from *T. stejnegeri*, cause fibrinogenolysis and fibrinolysis and possess hemorrhagic activity. They are also weak anticoagulants and inhibit platelet aggregation (α-fibrinogenase). In vitro studies, the venom has two opposite actions on the platelet: an increase in platelet aggregation activity in venom concentrations ranged from 1 to 30 μg/ml, while the activity gradually declined at concentration of 30–1,000 μg/ml, which might be secondary to the coexistence of platelet aggregation inhibitors in the venom (e.g., fibrinogenases, 5′-nuecleotidase, phospholipase A)

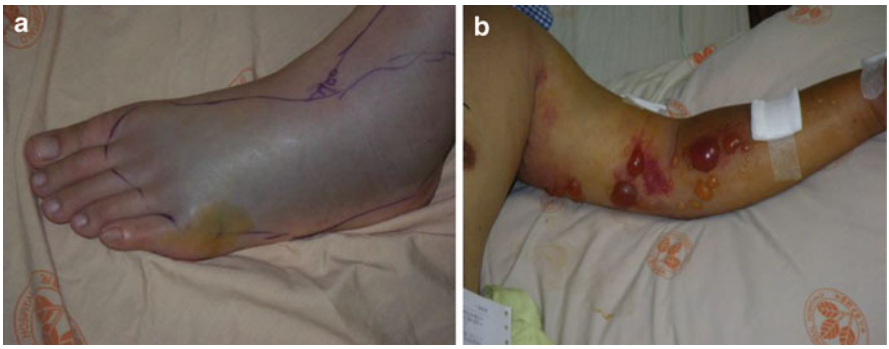

Fig. 2.4 (**a**) Patient was bitten by *P. mucrosquamatus* on the foot 8 h earlier. (**b**) Patient was bitten by *P. mucrosquamatus* on the left hand; bullae formation and marked tissue swelling were observed within 24 h

(Ouyang and Teng 1978). In animal studies, the venom causes a drop in platelet counts (Ouyang and Teng 1978), possibly due to platelet aggregation.

For better understanding of hematological derangement, Li et al. measured the maximum platelet aggregation rate (MAR) and antithrombin III and α2-plasmin inhibitor activities, both sensitive parameters for disseminated intravascular coagulopathy (DIC), as well as the fibrinogen level and fibrinogen degradation products (FDPs) in three cases of *T. stejnegeri* and one case of *P. mucrosquamatus* envenoming (Li et al. 2000). The study revealed that MAR was unchanged in *T. stejnegeri* envenoming but lowered in *P. mucrosquamatus* envenoming; antithrombin III activity, α2-plasmin inhibitor activity, and the fibrinogen level were lower in all four cases; and FDPs were elevated in *T. stejnegeri* envenoming. Therefore, low-grade DIC may be present in both snake envenomations.

(c) **Clinical manifestations**

Although the clinical manifestations of *T. stejnegeri* and *P. mucrosquamatus* bites are similar, envenomations caused by *P. mucrosquamatus* bite are usually more severe (Fig. 2.4) because the latter is bigger in size and the venom contents are higher (Liau and Huang 1997). The symptoms and signs of envenoming of both snakes include local swelling, pain, bruising, wound bleeding, cellulitis, necrosis, coagulopathy, rhabdomyolysis, acute renal failure, or compartment syndrome. Chen et al. studied 149 cases of *P. mucrosquamatus* bites; the frequency of bruising (75 %), cellulitis (26 %), necrosis (11 %), and rhabdomyolysis (11 %) was significantly higher than that in *T. stejnegeri* bites. The incidence of coagulopathy (6 %) was also higher but did not reach statistical significance (Chen et al. 2009). Similar to *T. stejnegeri* bite, there was occasional occurrence of bruising distant away from the bitten area; however, significant wound bleeding or bleeding into vital organs was neither observed.

Deinagkistrodon acutus

(a) **Distribution**

D. acutus is found in southern China, northern Vietnam, and possibly Laos. In Taiwan, it is distributed in mountainous or forested areas, in covered rocky or hilled regions.

(b) **Venom**

Both procoagulants and anticoagulants had been isolated from the venom of *D. acutus*, including thrombin-like enzyme (TLE), anticoagulant principles, prothrombin activation inhibitor, α-fibrinogenase (Cheng and Ouyang 1967; Ouyang et al. 1982a), as well as platelet aggregation inhibitor and hemorrhagins (Mori et al. 1984; Ouyang and Huang 1986; Xu et al. 1981). The procoagulant effect was caused by a thrombin-like action on fibrinogen (Ouyang 1957). TLE can also induce fibrinolysis in addition to fibrinogenase (Ouyang et al. 1972, 1982b). The anticoagulant principles, on the other hand, inactivate prothrombin, tissue factor, and coagulation factor V (Ouyang and Teng 1973; Ouyang et al. 1982b). The combination of the above-noted effects results in retardation of blood clotting in vivo studies (Ouyang and Teng 1976). Moreover, some other proteins (e.g., hemorrhagins, metalloproteinase, protease, and hyaluronidase) play crucial roles in vascular injury and local toxic effects. All of the actions lead to clinically significant bleeding and tissue damage in *D. acutus* envenomations.

(c) **Clinical manifestations**

D. acutus bites have been rarely observed in Taiwan, with only a few cases being reported in the English literature. A 10-year-old girl bitten by *D. acutus* on her left hand was reported in 1969 (Kuo and Wu 1972). The patient developed fever, bleeding tendency, and multiple dark reddish vesicles on the left hand in spite of treatment with traditional medicine. She was transferred to a medical center 27 h later. On presentation, continuous oozing from the wound, bleeding from the nose, gingival, and eponychium were noticed. The left hand was rigid and could not be moved due to painful swelling. Laboratory examination revealed blood hemoglobin (Hb) 7.9 g/dl, and the bleeding time was prolonged for more than an hour without clotting. The patient received a vial of monovalent antivenom for *D. acutus* with good response. The bleeding time soon normalized, and oozing from the wound discontinued 12 h after the infusion of antivenom. The patient received local wound debridement and skin grafting 3 weeks later. The pathological findings of the wound at 40 h post-bite revealed epidermal layer fragmentation and cleavage by edema, infiltration of the deeper dermis by neutrophils and lymphocytes, and extravasation with engorged blood vessels. The patient recovered with limited movement of left thumb.

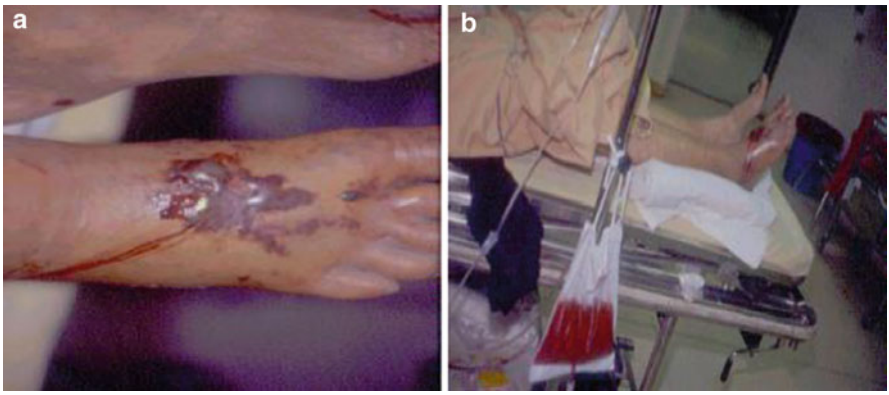

Fig. 2.5 (**a**) Patient was bitten by *D. acutus* on right foot. Continuous bleeding from the fang marks and hemorrhagic bullae formation were observed 5 h post-bite. (**b**) Continuous bleeding from the wound and gross hematuria 12 h after the bite (the same case as Fig. 2.5a)

The second case was a 16-year-old girl bitten by *D. acutus* on right palm in 1977 (Shen 1983). The patient developed generalized petechia and persistent oozing from the bite wound, had near syncope, and was sent to a hospital 28 h post-bite. On examination, the swelling had extended to the shoulder. Her blood was incoagulable with prothrombin time (PT) and activated partial thromboplastin time (aPTT) both exceeding 300 s, and the fibrinogen level was immeasurable. For unknown reasons, the patient received 4 vials of bivalent antivenom for *T. stejnegeri* and *P. mucrosquamatus* rather than monovalent antivenom for *D. acutus* and whole blood transfusion of 1,500 ml in the following 3 days. On day 6, the patient's Hb level was 7.2 g/dl, platelet count was 169,430/mm^3, and bleeding time was 4 min. On day 8, the patient received 10 units of plasma and then went home against medical advice. The patient was still alive after 6 years at a medical follow-up.

The third case was a 44-year-old male bitten by *D. acutus* on the dorsal aspect of the left middle finger in 1991 (Hung et al. 1997). Swelling, subcutaneous ecchymosis, hemorrhagic blisters, and oozing from the wound developed a few minutes later. The patient was sent to a hospital where two vials of bivalent antivenom for *T. stejnegeri* and *P. mucrosquamatus* were administered due to the unavailability of monovalent antivenom for *D. acutus*. After 44 h, the patient went to another hospital because of persistent pain, progressive swelling, ecchymotic change in left forearm, and continuous bleeding from left hand. In the emergency department, severe thrombocytopenia (blood platelet count 2,000/mm^3) was noted, and bivalent antivenom was administered again in addition to fresh frozen plasma and platelet replacement. Monovalent antivenom for *D. acutus* was administered 59 h post-bite after consulting PCC-Taiwan. The blood platelet count rose to 10,000/mm^3 6 h after the antivenom was administered and returned to a normal level 2 days later. Unfortunately, the compartment syndrome of left forearm and gangrenous change in left middle finger developed. The patient later received left forearm fasciotomy and amputation of left middle finger with fair wound healing. The typical findings of *D. acutus* envenoming are shown in Fig. 2.5.

Zhao and Rao studied 111 cases of *D. acutus* bite during 1974–1980 in southern China. Envenomation caused various degrees of hemorrhagic symptoms, local tissue swelling, and pain, skin ulceration, necrosis, or even shock (Zhao and Rao 1982). Hemorrhagic diathesis included bleeding from the wound (64.9 %), mouth, nose (41.4 %), and subcutaneous tissues (61.3 %). In addition, skin or deep tissue necrosis might develop 3–5 days later. Li et al. reported a case of *D. acutus* envenomation with hemostatic disturbance 22 h after snakebite and found that antithrombin III and α2-plasmin inhibitor activities were depressed, while undetectable fibrinogen and elevated FDPs were noted in blood. *D. acutus* envenomation causes significant DIC (Li et al. 2000).

Daboia russelli siamensis

(a) **Distribution**

D. r. siamensis, a true viper, is found in Myanmar, Thailand, Cambodia, southern China, and Indonesia. In Taiwan, it has a scattered distribution in the southern part of the country and in the eastern side of the central mountain range, at lower altitudes below 1,500 ft. It is a nocturnal species and is found mainly in open or dry habitat.

(b) **Venom**

Wuster et al. examined the morphology of *Daboia russelli* (referred to as *Vipera russelli*) and reclassified them into two subspecies: a western subspecies (*D. r. russelli*), which includes populations formerly known as *D. r. russelli*, *D. r. nordicus*, and *D. r. pulchella*, and an eastern subspecies (*D. r. siamensis*), which includes the populations formerly assigned to *D. r. siamensis*, *D. r. formosensis*, *D. r. limitis*, and *D. r. sublimitis* (Wuster et al. 1997). There is much variation in venom composition and clinical effects both between and within the subspecies. The venom of *D. r. siamensis* contains several toxic components including procoagulants, which can activate coagulation factors V and X, phospholipase A_2 (PLA_2), proteinases (e.g., metalloproteinase), anticoagulants, and others (Risch et al. 2009). The procoagulants can induce widespread intravascular fibrin formation and consumptive coagulopathy. They also adversely affect the renal hemodynamics in studied animals in addition to inducing fibrin deposition in the renal microvasculature (Suntravat et al. 2011). The major lethal component, PLA_2, produces presynaptic neuromuscular blocking activity, edema-inducing activity, myonecrotic activity, and indirect hemolytic activity (Lee 1948; Maung Maung et al. 1995; Wang et al. 1992). The isoenzymes also cause unfavorable renal hemodynamics and platelet aggregation (Mitrmoonpitak et al. 2013; Suwansrinon et al. 2007). The metalloproteinases might degrade the extracellular matrix proteins, damage the integrity of blood vessels, and induce local wound bleeding (Mitrmoonpitak et al. 2013). In animal studies, rapid cardiac arrest resulted from intravascular clotting occurred when the venom was injected

intravenously. On the contrary, the animals usually died from neuromuscular blockade or consumptive coagulopathy when the venom was administered subcutaneously (Aung-Khin et al. 1977; Lee 1948). The overall pathological effects of the venom depend on the amount of each component, the route of administration, and individual susceptibility (Aung-Khin et al. 1977).

(c) **Clinical manifestations**

There is fascinating geographical variation in the clinical manifestations of Russell's viper bites. Conjunctival edema is unique to Myanmar, acute pituitary infarction to Myanmar and south India, and rhabdomyolysis and neurotoxicity to Sri Lanka and south India (Warrell 1989). Hung et al. studied 18 cases of *D. r. siamensis* bites during 1987–1999 and concluded that the most prominent effects of *D. r. siamensis* envenoming in Taiwan were coagulopathy and renal dysfunction (Hung et al. 2002). The clinical manifestations of *D. r. siamensis* envenoming included local pain, ecchymosis, and/or bleeding at the bitten site in 17 cases; mild swelling limited to 1 joint area in 15 cases; systemic bleeding in 13 cases, including gastrointestinal tract (10), genitourinary tract (11), lung (5), or central nervous system hemorrhage (1); thrombocytopenia, acute renal failure, and hemolysis in 13 cases; ecchymosis at distant site in 11 cases; coagulopathy in 10 cases; rhabdomyolysis in 9 cases; wound necrosis in 3 cases; and arterial thrombosis in 2 cases. There was a case of a dry bite and 3 out of the 18 cases died (17 %). Local effects caused by *D. r. siamensis* bites were less severe compared with those caused by other venomous snakebites in Taiwan. After systemic envenomation, coagulopathy, including PT and aPTT prolongation, usually developed within 1.8–4.6 h post-bite. Coagulopathy subsided 3 h to 2 days after the administration of specific antivenom. Thrombocytopenia usually developed within 2–30 h and platelet level returned to normal 1–3 days after the administration of antivenom (Chen et al. 1997). Acute renal failure usually developed within 3 h to 6 days post-bite; however, most of these cases had oliguria on the first day after envenoming. Nine of 13 cases of acute renal failure necessitated renal replacement therapy, with gradual recovery of renal function in 13–61 days. Notably, eight cases were unconsciousness on the first day after a bite. Four of these cases spontaneously recovered in the successive days; however, the other two had cerebral infarction and the remaining two died without determination of the central nervous system pathology. There was no neuromuscular blocking effect, except for slight dizziness or local numbness after envenoming in human cases.

Hung further investigated renal pathology after *D. r. siamensis* envenoming in dogs. Renal injury was observed as early as 30 min after envenoming (Hung and Lin-Shiau 2001). In a phase 2 study involving 13 patients, renal dysfunction was milder in cases that received monovalent antivenom within 6 h of envenoming than those who received antivenom after 6 h (Hung et al. 2006). Based on these findings, Hung et al. suggested that 2–4 vials of monovalent specific antivenom should be administered as soon as possible after envenomation (Hung et al. 2006). The typical findings of *D. r. siamensis* envenoming are shown in Fig. 2.6.

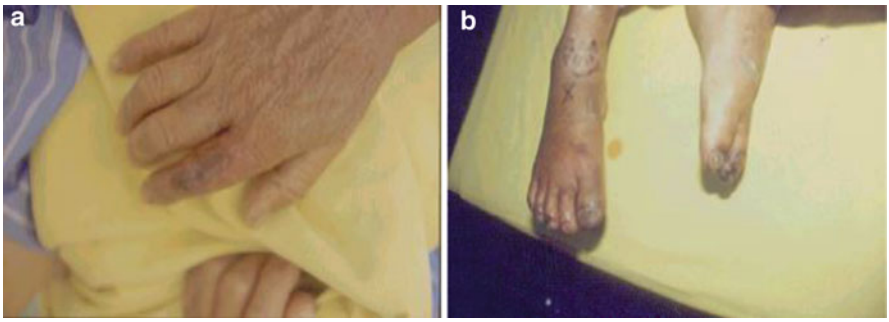

Fig. 2.6 (**a**) Patient was bitten by *D. r. siamensis* on right index finger, and local necrosis was noted on the bitten site. (**b**) Patient developed gangrenous change over toes of both lower legs 36 h later (the same case as Fig. 2.6a)

Naja atra

(a) **Distribution**

N. atra is found in southeastern China, northern Laos, and northern Vietnam. It is distributed throughout Taiwan at low altitudes and is more common in the west central and southern parts of the country.

(b) **Venom**

The venom of the *N. atra* consists of at least 100 proteins and peptides including cardiotoxins (cytotoxin), neurotoxins (cobrotoxin), hemotoxins, phospholipase A_2 (PLA_2), and other proteins (Li et al. 2004). The cardiotoxins and neurotoxins are the major components, which account for 55 % and 10 % of the dry weight of crude venom, respectively (Hung et al. 2003). The most toxic fraction to small animals was shown to be neurotoxins, which caused neuromuscular blockade and respiratory failure (Lee 1995). However, the most prominent effect of *N. atra* envenoming in humans is bite wound necrosis. The cardiotoxins may act individually or synergistically with other proteins (e.g., PLA_2) to induce local tissue necrosis through complex and poorly understood mechanisms (Fletcher and Jiang 1993; Kao et al. 2009a, b), whereas neurotoxins or PLA_2 alone do not (Lee 1995). In rabbits, local tissue necrosis was visible within 1 h after subcutaneous injection of 0.3–1 mg crude venom (Fukuyama and Sawai 1972) or 4 h in humans after a bite (Hung et al. 2003).

(c) **Clinical manifestations**

In a PCC-based study during 1986–1998, 43 cases of *N. atra* injury, including 36 bites and 7 spit ophthalmia, were analyzed (Lee et al. 2000). The clinical effects were local swelling and pain in 94.4 % of patients around the bitten area, wound necrosis in 25 %, fever in 22.2 %, and limb numbness in 13.9 %; miscellaneous

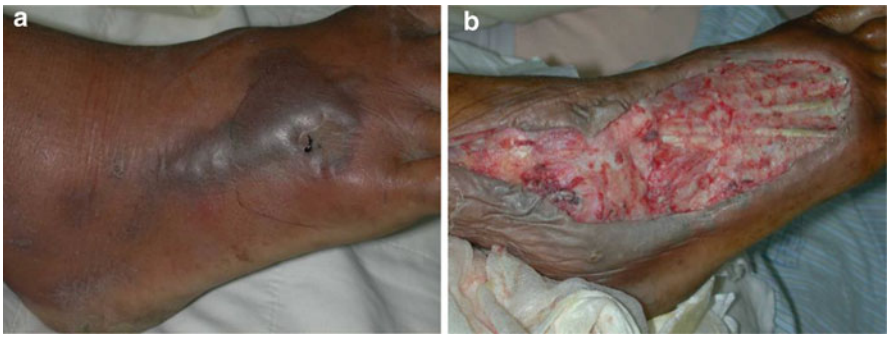

Fig. 2.7 (**a**) *N. atra* snakebite on right foot, local tissue necrosis and bullae developed 12 h later. (**b**) Debridement was performed 5 days after the bite (the same case as Fig. 2.7a)

effects such as transient hypotension, headache, dizziness, throat ache, dyspnea, ecchymosis, and blister or bullae formation around the wound or wound bleeding were less frequently reported (2.8 % –8.3 %). In the seven spit ophthalmia cases, all developed conjunctivitis and one case had headache and vomiting. All of them recovered well after conservative and local treatment.

Mao and Yang studied 119 *N. atra* bites from two medical centers (Mao and Yang 2013). Swelling and cellulitis were the most commonly observed clinical effects (94.1 % and 72.2 %, respectively), followed by wound necrosis (63 %), fever (43.7 %), necrotizing fasciitis (39.5 %), local numbness (28.6 %), and blisters or bullae formation (17.6 %) around the wound or compartment syndrome of the bitten limb (1.7 %). A few cases (32/52) developed temporary gastrointestinal effects such as nausea, vomiting, abdominal upset, or diarrhea shortly after envenoming. Systemic neurotoxicity manifested as transient/mild weakness or ptosis was only observed in only 5 of 115 cases (4.3 %; 2 weakness, 3 ptosis). Dry bite was recorded in 6.3 % of cases. No death occurred during the study period.

The typical findings of *N. atra* envenoming are shown in Fig. 2.7.

Bungarus multicinctus

(a) **Distribution**

B. multicinctus is found in mainland China, Myanmar, Laos, and northern Vietnam. It is very common in Taiwan. It is distributed at lower altitudes throughout the country, possibly below 2,000 ft.

(b) **Venom**

The venom of *B. multicinctus* contains several neurotoxins, including α- and β-bungarotoxins and muscarinic toxin-like proteins. α-Bungarotoxin binds to post-synaptic acetylcholine receptor in the motor end plates with high affinity, producing

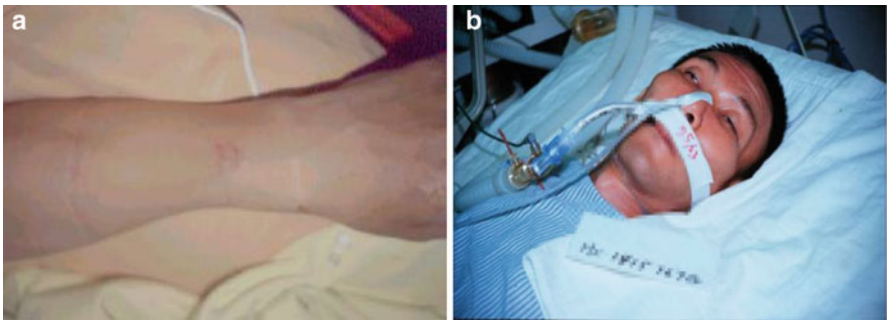

Fig. 2.8 (**a**) Patient was bitten by *B. multicinctus* on the forearm without overt local effects. (**b**) Respiratory paralysis occurred 5 h after the bite necessitating intubation and mechanical ventilation. Ptosis is also present (the same case as Fig. 2.8a)

essentially irreversible neuromuscular blockade; on the other hand, β-bungarotoxin acts presynaptically to depress acetylcholine release from the nerve endings (Pe et al. 1997). β-Bungarotoxin is a basic protein, consisting two subunits named A-chain, the active subunit, with phospholipase A_2 activity, and B-chain, which may function as an affinity probe to guide the toxin to its target on nerve terminals (Rowen 2001). β-Bungarotoxin causes damage of motor nerve terminals, change in the numbers of synaptic vesicle, and mitochondrial uncoupling and synergistically with other bungarotoxins, leading to neuromuscular blocking effect. Its toxicity seems to parallel the phospholipase A_2 activity (Abe et al. 1977). Although κ-bungarotoxin and γ-bungarotoxin have been described, their toxicological activities and clinical significance are less extensively studied (Chiappinelli 1991; Endo and Tamiya 1991).

(c) **Clinical manifestations**

The victims of *B. multicinctus* envenomations usually have typical neurological manifestations, including ptosis; ophthalmoplegia; paralysis of jaw, tongue, and deglutition; respiratory paralysis; quadriparesis; and parasympathetic abnormalities upon envenomings (Chan et al. 1995; Pe et al. 1997). Paralytic symptoms usually develop within a few hours (0.5–4 h) and the local symptoms were minimal (Kuo and Wu 1972; Pe et al. 1997). In the literature, the intervals between *B. multicinctus* bite and death of victims not treated with antivenom ranged from 6 to 30 h, while natural recovery from paralysis ranged from 8 to 30 days when mechanical ventilation was initiated in a timely manner (Chan et al. 1995; Pe et al. 1997).

Apart from the typical neurological effects, a life-threatening hyponatremia syndrome was recently described in a case of *B. multicinctus* envenoming in Vietnam, the mechanisms of which remain unclear (Hojer et al. 2010). Therefore, electrolytes should be carefully monitored in cases of *B. multicinctus* bites in addition to serial neurological examinations.

The typical findings of *B. multicinctus* envenoming are shown in Fig. 2.8.

Diagnosis

Snakebite is an occupational and environmental disease. In Taiwan, this health problem is complicated by the fact that snakes from different genera and species are commonly found in the same geographic area. Although there are typical findings of the six medically important venomous snakebites, either by clinical or laboratory tests (e.g., PT, aPTT, renal function), it may not be easy to distinguish between them upon bites instantly due to the similarity of early local manifestations. Currently, there is no commercialized rapid venom detection kit available in Taiwan. Misdiagnosis or inability to identify the culprit snake species thus frequently occurs in the emergency department (ED), accounting up to 45 % of all venomous snakebites (Liang et al. 1992). Hung et al. developed a sandwich-type enzyme-linked immunosorbent assay for the measurement of *N. atra* venom in biological samples in the early 2000s and obtained 1 ng/ml of detection limit in both urine and serum specimens (Huang et al. 2002, 2003). Using this method could quickly and successfully confirm the diagnosis of *N. atra* snakebites initially mistaken to be *P. mucrosquamatus* snakebites. The authors also developed a quick test for *N. atra* venom detection in 20 min by using immunochromatographic method. However, further validation of the applicability of this immunoassay in human cases is still needed. Moreover, the development of similar assays for other medically important venomous snake species is desirable.

Management

First Aids

Several measures have been described in the management of snakebites; however, many of them are controversial or even harmful. Arterial tourniquet, incision and suction, electrotherapy, and cryotherapy are no longer recommended (McKinney 2001). The effectiveness of constriction band and pressure immobilization also necessitates further evaluations in Taiwan.

Constriction Band or Pressure Immobilization

A constriction band, designed for crotalid snakebites in North America, is an elastic bandage, thick rope, or piece of clothing circumferentially wrapped above the site of snakebite to exert a pressure great enough to occlude venous or lymphatic return (McKinney 2001). It is typically recommended when the victim is more than 2 h driving distance away from a hospital and less than 30 min has elapsed since the bite. Once the patient arrives at the hospital, if there is no sign of envenomation, the constriction band should be removed. If the patient has evidence of systemic toxicity on arrival at the hospital, antivenom should be administered before the constriction band is loosened.

The pressure immobilization (PI) method, which originated in Australia mainly used in elapid envenomations, has two components: the affected extremity is firmly

wrapped with an elastic bandage, and equally important, the entire extremity is then splinted (Pearn et al. 1981). The tightness of the wrap is defined as a pressure between 40 and 70 mmHg in the upper extremity and 55–70 mmHg in the lower extremity. However, there is insufficient evidence of their efficacy in the management of various types of snake envenomations in other countries. In 2011, six toxicological organizations have made a position statement: PI is not recommended for prehospital treatment of North America Crotalinae snakebites (ACMT et al. 2011). In Taiwan, given the fact that the prehospital transportation time is fairly short (e.g., within 30 min) (Hu et al. 1996; Lin et al. 1998) and trapping the highly cytotoxic venom of snakes at the bitten site using these measures may even worsen local necrosis (McKinney 2001), rest prior to transportation is probably the only management that is recommended in the prehospital setting.

Incision and Suction

The recommendation of incision and suction is accompanied by multiple qualifications: incisions 3 mm deep, 1 in. long, only if more than 30–40 min from reaching a healthcare facility, within 5 min of the snakebite with clear signs of envenomation, and with incisions made longitudinally on the extremities (Hall 2001). Evidence from animal models suggests that incision and suction can remove 1 % to >50 % of injected venom if applied within minutes of injection and may improve survival in some cases (McKinney 2001). In humans, however, laceration of tendons, nerves, and arteries, wound deterioration, and an increased infection rate from these attempts have been reported (Hall 2001). Given the fact that mortality from snakebites in Taiwan is uncommon and the most important principle of first aids is "do no harm," this technique is not recommended.

Electrotherapy or Cryotherapy

Guderian et al. reported local application of high-voltage (25 kV), low-amperage (<1 mA) direct electric current to human cases, with the bitten area electrically grounded, for the treatment of venomous snakebites in Ecuador in the 1980s (in particular, *Bothrops atrox*, *B. bilineatus*, *B. nasutus*, *B. schlegelii*, *B. castelnaudi*, and *Lachesis muta*) (Guderian et al. 1986). When applied to a reconstituted *Crotalus atrox* venom solution, direct electric current at low voltage showed neutralizing properties against venom phospholipase A_2 and metalloproteinases (Panfoli et al. 2007). However, it has been found to be ineffective in animal models of envenomation. Complications of this therapy, including burns, myocardial infarction, and seizures, have been reported in humans. As such, electrotherapy is contraindicated in the treatment of venomous snakebites (McKinney 2001).

Cryotherapy, which involves packing or immersion of the bitten limb in ice or ice water, was thought to be beneficial by slowing the spread of the venom, lowering enzymes activity, and thus decreasing the severity of envenomation (Mullins and Naylor 1960). This approach has become less popular over the past 40–50 years because experimental models have failed to demonstrate its effectiveness. There were some cases of sustained tissue loss, amputations, or permanent disability after prolonged cryotherapy. An ice pack intermittently placed on a bite

for pain control, similar to that used in case of an ankle sprain, is less likely to be harmful; however, more aggressive cryotherapy or ice therapy is contraindicated (McKinney 2001).

Summary of First Aids

There are no definitive data on prehospital management of snakebites in Taiwan. Given the fact that prehospital transportation is expeditious and the most effective therapy for snake envenomation is the timely administration of antivenom, any first aid procedure leading to delayed transportation should be scrutinized. At present, the following recommendations, described by Seifert et al. in 2011, are encouraged: (1) remove jewelry (e.g., rings on the bitten finger) and loosen tight-fitted clothing on the bitten limb; (2) loosely splint or immobilize the limb in a functional position, while the other potential actions should be guided by an experienced clinician; (3) maintain the bitten limb in a neutral position with regard to the heart; (4) get to a hospital, preferably transported by an EMS provider (in general, supine positioning will aid providers in managing possible effects such as hypotension or vomiting); and (5) avoid useless or potential harmful interventions such as arterial tourniquet, incision and suction, electrotherapy, or cryotherapy (Seifert et al. 2011).

In-Hospital Management

Antivenom and Its Side Effects

Four types of antivenom, all $F(ab')_2$ fragment in the lyophilized form, are available in Taiwan, namely, a bivalent antivenom against *T. stejnegeri* and *P. mucrosquamatus*, a bivalent antivenom against *N. atra* and *B. multicinctus*, a monovalent antivenom against *D. acutus*, and a monovalent antivenom against *D. r. siamensis*. Liau and Huang studied the dry weight of venom milked from the six medically important venomous snakes, calculated the median lethal dose (LD_{50}) of different snake venoms, and estimated the average dosage of antivenom required for neutralization (Table 2.1) (Liau and Huang 1997). Based on previously published studies and clinical observations, PCC-Taiwan formulated a flowchart for the management of snakebites (Fig. 2.9). The recommended dosage of relevant antivenom to treat a moderate-to-severe envenoming is 1–2 vials for *T. stejnegeri,* 2–4 vials for *P. mucrosquamatus,* 2–4 vials for *D. acutus,* 2–4 vials for *D. r. siamensis*, 6–10 vials for *N. atra*, and 2–4 vials for *B. multicinctus* bites (Hung et al. 1999). Moreover, PCC-Taiwan recommends completely filling each vial with 20 ml diluent and suggests all the antivenom should be administered intravenously at an infusion rate of 1–2 ml/min, which is based on pharmacokinetic studies on antivenom (Hung et al. 1999).

Antivenom was once used reluctantly due to the fear of developing adverse reactions and the uncertainty about its effectiveness (Sawai and Tseng 1969). Although the incidence of adverse reactions was not comprehensively evaluated in early studies, it is quite uncommon nowadays. In the past, the Vaccine Center in Taiwan adopted the Tanaka method to obtain sera from horses; however, two-thirds

Table 2.1 Amount of venom extracted by milking of 6 medically important venomous snakes and recommended doses of antivenom (Hung et al. 1999; Liau and Fuh 1991; Liau and Huang 1997)

Snake species	No. of specimen	Amount of envenoming of each snake (mg)		LD_{50} (μg/g mice)	Antivenom			
		Mean ± SE	Range		Neutralizing activity (mg/unit)	Average dose of antivenom (vials)	Type (2,000 units/vial)	Recommended dose (vials)
T. stejnegeri	115	6.9 ± 3.1	0.6–30.3	2.0 ± 0.23	0.013	0.3	Bivalent	1–2
P. mucrosquamatus	124	33.4 ± 15.5	6.6–125	2.9 ± 0.61	0.0195	0.9	Bivalent	2–4
D. acutus	103	105 ± 52	16.7–460	4.9 ± 0.41	0.026	2	Monovalent	2–4
D. r. siamensis	53	18.4 ± 10.3	4.7–83.2	0.29 ± 0.05	0.00247	NA	Monovalent	2–4
N. atra								
Eastern origin	45	217 ± 88	76.5–574	0.67 ± 0.02	0.00871	12.5	Bivalent	6–10
Western origin	107	48.0 ± 19.6	23.4–120	0.33 ± 0.01	0.00429	5.6	Bivalent	
B. multicinctus	118	4.4 ± 2.3	0.5–13.6	0.1 ± 0.02	0.001	2.2	Bivalent	2–4

1 unit antivenom neutralizes 1 LD_{50} in a 13 ± 0.5 g mouse/I.P.; LD_{50}: median lethal dose
NA not available

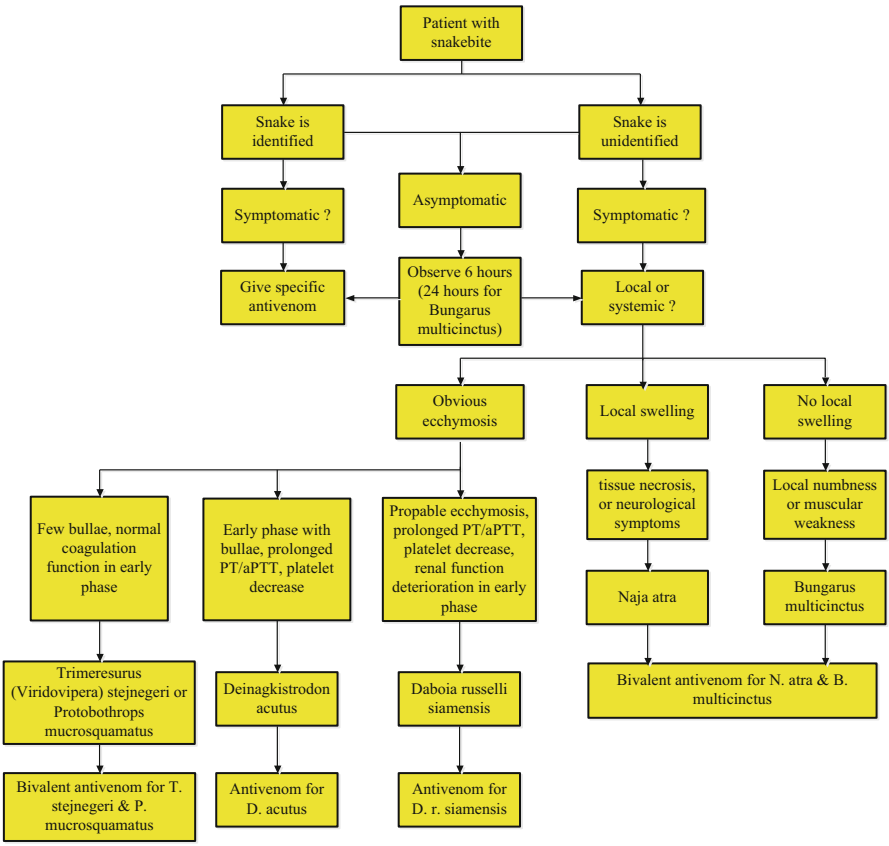

Fig. 2.9 Flowchart of the management of six medically important venomous snakebites in Taiwan (Hung et al. 1999)

of the horses failed to produce a satisfactory titer of neutralizing antibody. Thus, the manufacturing process has undergone several modifications since the 1980s (Huang et al. 1985, 1986). At present, horses are immunized with glutaraldehyde-attenuated venom toxoid and Freund's adjuvant (Liau and Huang 1997). When the plasma antibody titer reaches a plateau, the horse blood is withdrawn into a container with sodium citrate as an anticoagulant. The plasma is then processed by sedimentation and digestion with pepsin. Ammonium sulfate is repeatedly added during the purification process to precipitate the nonimmune protein. Finally, the mixture is filtered and the immune protein pellet is collected and press-dried on a filter paper. The obtained immunoglobulin fragment $F(ab')_2$ is redissolved in a buffer containing 0.01 % thimerosal and 2 % glycine. After sterilization, the antivenom is lyophilized, sealed in vacuum, and stored in 20-ml serum vial. The antivenom powder, with a shelf life of 5 years, is best stored at 4 °C before use (Huang et al. 1985, 1986). The newer immunization protocol is highly effective and safer

for horses compared with the conventional Tanaka method. Potent antivenom is obtained after an immunization period of 2 months instead of 6 months. There are 2,000 units per vial of antivenom (or at least 1,000 Tanaka units), and 1 unit neutralizes 1 LD_{50} of specific venom intraperitoneally injected in a mouse weighting 13 g (Liau and Fuh 1991).

Several molecular mechanisms account for the development of adverse reactions during antivenom infusion, including anaphylaxis mediated by IgE, anaphylactoid reaction caused by complement system activation, or pyrogenic response to contaminated endotoxins. The reported incidence of early adverse reactions secondary to the administration of ammonium sulfate-precipitated whole IgG or $F(ab')_2$ antivenom ranged from 10 % to 87 % (Otero et al. 1999). In Taiwan, studies on antivenom-related adverse reactions are sparse. Chen et al. examined 130 cases of snakebites and found that 32.3 % developed a positive antivenom skin test (Chen et al. 2000a). Following pretreatment with antihistamine and hydrocortisone, one patient (0.7 %) eventually had a skin rash amenable to conservative treatment. In a different study, Chen et al. investigated 179 cases of crotalid snakebites (*T. stejnegeri* and *P. mucrosquamatus*). Seventeen percent of the patients developed positive antivenom skin tests; however, allergy responses occurred only in 3 % of the patients with negative skin tests (Chen et al. 2007a). Otherwise, no serious antivenom reactions were recorded in either study.

There is hardly any information about the incidence of delayed allergic response. Two cases of serum sickness after receiving bivalent antivenom for *T. stejnegeri* and *P. mucrosquamatus* had been reported in the English literature (Huang et al. 2010; Ko and Chung 2013). The survey conducted by Shih et al. revealed that a patient had anaphylaxis after receiving bivalent antivenom for *N. atra* and *B. multicinctus* injection and two patients possibly had serum sickness. However, the relevant medical history was lacking (Shih et al. 2006). In Taiwan, the antivenom skin test is still advocated by the manufacturer because of medicolegal issues, and it is a common practice in hospitals regardless of plentiful evidence that suggests the low probability of adverse reactions of antivenom and the unreliability of skin test.

For more than 100 years, horses were used in the production of antivenoms; therefore, many people are sensitive to horse sera and may develop anaphylaxis after a second contact. The development of an avian-derived yolk immunoglobulin (IgY or truncated version of IgY) against snake venom has been evaluated in Taiwan. Lian et al. preliminarily studied the egg yolk IgY production in "big Kaiya" ducks immunized with *N. atra* venom toxoid (Lian et al. 2004). The duck was immunized with venom toxoid every 2 weeks, and the antibody titer reached a stable level between 5 and 21 weeks. The antibody amount harvested from 8 eggs during this period is comparable with that present in one vial of antivenom derived from horses. Chiou further estimated the antibody productivity from duck egg yolk to be more efficient than that from horses (egg yolk, $>$500 mg/kg body weight/month; horse serum, $<$200 mg/kg body weight/month) (Chiou 2008). Considering workers' safety, animal welfare, the cost of antivenom production, and possible allergy to horse sera, the development of avian-derived immunoglobulin against

snake venom seems to be attractive. However, all antivenoms derived from foreign proteins are capable of producing acute and delayed hypersensitivity responses. Healthcare providers must be aware of the possibility of life-threatening reactions resulting from the use of these products and be prepared to effectively treat a reaction should one occur.

Antivenom in Special Population

Chen et al. reported three pregnant women bitten by *T. stejnegeri* at 8, 17, and 28 weeks of gestation (Chen et al. 2007b). One of them received 1 vial of bivalent specific antivenom and 1 received 13 vials, while the other did not receive antivenom because her symptoms were mild. Fetal monitoring of these cases did not reveal evidence of fetal distress, and there was no maternal vaginal spotting. After delivery, follow-up of the children at 6, 8, and 10 years of age revealed no growth abnormalities. The author speculated that the safety of antivenom for pregnant patients is similar to that for other adults.

Wang et al. investigated snakebites in children and adolescents during 1994–2007 based on the database of Taichung Veterans General Hospital (Wang et al. 2009). There were 35 envenoming cases in patients aged between 2 and 18 years, with a median age of 9.5 years. The offending snake was *N. atra* in 11 cases, *T. stejnegeri* in 7, *P. mucrosquamatus* in 5, *D. acutus* in 1, and unknown venomous snakes in 11. In the study, the dose of bivalent antivenom for *T. stejnegeri* and *P. mucrosquamatus* and that for *N. atra* and *B. multicinctus* administered to snakebite patients ranged from 1 to 11 and 2 to 12 vials, respectively. No cases developed anaphylaxis in that study, whereas 3 patients had skin rashes amenable to treatment with antihistamine and steroids. Although none of the patients died, 5 of them underwent surgical intervention for wound necrosis caused by *N. atra* envenoming. The author speculated that the antivenom dosage recommended for adults may be equally safe for children and adolescent patients.

Antibiotic Therapy

Routine use of prophylactic antibiotics in snakebite cases is generally not recommended unless wound infection has occurred (Kerrigan et al. 1997). However, the venom itself may cause local reactions (e.g., tenderness, heat, swelling), fever, or elevated white blood cell counts that resemble wound infection during a bite (Blaylock 1999). Thus, the differentiation between wound infection and envenoming is difficult or even impossible in the early stages post-bite. In Taiwan, prophylactic antibiotic prescription is still a common practice in the management of snakebites. In Chen's study, 63 % *T. stejnegeri* and 76 % *P. mucrosquamatus* bites received prophylactic antibiotics; however, only 6 % and 26 %, respectively, developed clinically suspected cellulitis or wound infection (Chen et al. 2009). Chen et al. evaluated the bacteriology of snakebites in 21 patients with positive wound cultures during 2001–2010 (Chen et al. 2011). The most common pathogens isolated from infected snakebite wounds were *Morganella morganii* and *Enterococcus* species. Among these cases, 17 were bitten by *N. atra,* 1 by *P. mucrosquamatus,* 1 by *T. stejnegeri*, and 2 by unknown snake species. Huang

et al. studied 17 cases of snakebites with positive bacterial culture during 2005–2007 (Huang et al. 2012). The most common 3 pathogens were *M. morganii*, *Aeromonas hydrophila*, and *Enterococcus* species. Among these, 16 cases were bitten by *N. atra* and 1 by *T. stejnegeri*. The authors concluded that most of the wound infections were caused by *N. atra* bites; thus, empirical antibiotics with quinolones, third generation of cephalosporins, piperacillin/tazobactam, and/or aminoglycosides for gram-negative pathogens, vancomycin or ampicillin for gram-positive pathogens, and metronidazole or clindamycin for anaerobic pathogens should be considered for the management of an infected wound caused by *N. atra* bite.

Mao and Yang analyzed 112 cases of *N. atra* envenomings from 2 medical centers and found that 86 (76.8 %) patients developed wound infection or cellulitis, 75 (67.0 %) had wound necrosis, and 47 (42.0 %) had necrotizing fasciitis (Mao and Yang 2013). In their study, bacterial cultures of wound discharge, necrotic tissues, or blood were obtained from 59 of the 86 cases. Fifty of the patients (84.7 %) had positive results, and more than 2 organisms (polymicrobial) were isolated from 32 (54.2 %) patients. Twenty-three organisms were recognized, and the most common pathogens were gram-negative rods, followed by gram-positive cocci. The species of bacterium isolated is *M. morganii* in 32 cases, *Enterococcus* spp. in 21, *Proteus* spp. in 8, *A. hydrophila* in 7, and the anaerobe *Bacteroides* spp. in 7. Although the choice of empiric antibiotics necessitates the bacteriology of snakebite to be determined first, there is no prospective evaluation of the optimal timing and choice of prophylactic antibiotics in the management of snakebites in Taiwan. Based on currently available data, we therefore suggest that antibiotics should be withheld for crotalid snakebite treatment unless wound infection has developed. Further studies of the effects of prophylactic antibiotic administration on the outcome of snakebites, especially *N. atra*, in Taiwan are warranted.

Surgery

The local effects of snake envenomation could result in significant tissue destruction such as local necrosis, necrotizing fasciitis, or even compartment syndrome. Shih et al. studied 118 cases of snakebites during 1999–2004. Among them, 16 required surgery, including 7 (of 14) *N. atra* bites, 5 (of 54) *P. mucrosquamatus* bites, 1 (of 29) *T. stejnegeri* bite, 1 *D. acutus* bite, and 2 (of 13) unknown snakes bites (Shih et al. 2006). The procedures performed were debridement in 11 cases, incision and drainage in 4, amputation of digit in 1, split-thickness skin graft in 4, and local or distant flap in 5. The surgical indications included wound necrosis, abscess formation, gangrene of digits, or necrotizing fasciitis. Early excision of the bitten wound was abandoned, and there was no prophylactic fasciotomy for crotalid snakebites. In the study, *N. atra* was significantly associated with a risk of surgery. Moreover, hospital stay was significantly longer in the surgical group than in the nonsurgical group (19.06 vs. 5.43 days, statistic significance was not specified).

Liao et al. evaluated 46 cases of snakebite during 1986–1999; 10 patients received necrotic tissue debridement and 3 of 5 ultimately requiring skin grafts

were bitten by *N. atra* (Liao et al. 2000). In a study of 112 cases of *N. atra* envenomation by Mao and Yang, surgery was performed in 61 patients (54.5 %) at a median of 4 days post-bite (interquartile range of 3–7 days) due to wound necrosis, abscess formation, necrotizing fasciitis, or, in rare cases, compartment syndrome (Mao and Yang 2013). Based on these limited case studies, most snakebite patients in Taiwan that underwent surgery were bitten by *N. atra*. Although early excisional therapy and prophylactic fasciotomy in the management of snakebites were no longer recommended (Cumpston 2011), the optimal timing of surgery, partly depending on the severity of local effects and secondary infectious complications, remains unknown, which warrants better-designed prospective studies in the future.

Summary of in-Hospital Management

According to the guideline proposed by the PCC-Taiwan, the recommended dosage of relevant antivenoms to treat a moderate-to-severe case of envenoming is 1–2 vials for *T. stejnegeri*, 2–4 vials for *P. mucrosquamatus*, 2–4 vials for *D. acutus*, 2–4 vials for *D. r. siamensis*, 6–10 vials for *N. atra*, and 2–4 vials for *B. multicinctus*. The antivenoms should be administered intravenously at an infusion rate of 1–2 ml/min. Prophylactic antibiotics are generally not required in crotalid snake envenomings (e.g., *T. stejnegeri* and *P. mucrosquamatus*) because of low incidence of wound infection, whereas they may be needed in patients with *N. atra* bite given that wound necrosis, abscess formation, gangrenous change of distal limbs, and necrotizing fasciitis are relatively common in such patients. The use of prophylactic and empirical antibiotics in *N. atra* bites should judiciously follow the results of bacteriologic studies. If the offending snake was not identified (e.g., snake escaped), management by or consultation with experienced experts is advised.

Conclusion and Future Directions

Snakebite is an environmental and occupational disease. A general knowledge of management against snake envenomations is necessary for the citizens, EMS providers, and clinicians. More researches on the severity assessment (e.g., severity score), risk factors for the development of severe disease, optimal dosing intervals of antivenom, effect of prophylactic antibiotics on the outcomes, and the timing of surgery of venomous snakebites are warranted in Taiwan. Further development of specific antivenom toward certain toxic venom fractions instead of polyvalent antivenom should be considered; however, it may not be cost-effective and analysis of more cases to determine the major effects of various snake venoms in humans should be established first.

Cross-References

► Epidemiology of Snake Envenomation in Taiwan

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