Snakebites in Hong Kong: how to face the possible changes?
毒蛇咬傷在香港：如何面對可能出現的變化？

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Introduction: Over the past years, the environmental and scientific changes have shaped the snakebite scenarios and will continue to do so. Their effects ahead are discussed. Incidence: Because of declining plant agricultural industry and rising urbanization, a falling incidence is reasonably expected in future. In order to maintain the knowledge and skills, training for clinicians will become more crucial. Venom detection kits: Kits for Naja atra and Cryptelytrops albolabris have been available overseas. Local data should be gathered regarding their clinical application. Antivenoms: The common local species covered by the haemotoxic and neurotoxic polyclonal antivenoms from Thailand is only Cryptelytrops albolabris. Introduction into Hong Kong is not recommended. Enzyme inhibitors: With an aim to improve the control of local injury that is unsatisfactorily accomplished by antivenoms, therapy with venom enzyme inhibitors is under research. Conclusion: A decreasing number of snakebite is anticipated. Venom detection kits should be explored for the use in appropriate cases. (Hong Kong j.emerg.med. 2011;18:217-220)

簡介：在過去的幾年，環境和科學的變化改變了傷蛇咬傷的情況，並會繼續不斷產生變化。我們對未來的影響作出了討論。發生率：由於農業生產之下降和不斷的都市化，未來發生率之下降是可預期的。為了維持相關的知識和技能，培訓醫師將變得更加重要。蛇毒測試劑：葉鏡額和青竹蛇測試劑已在海外使用。我們應收集有關臨床之本地數據。抗蛇毒血清：來自泰國的血液毒素和神經毒素多價抗蛇毒血清只覆蓋本地的青竹蛇品種，並不建議將其引進到香港。酶抑制劑：旨在控制不能用抗蛇毒血清處理的局部範圍的傷勢，而我們正在研究蛇毒酶抑制劑的治療效用。結論：毒蛇咬傷個案預期會減少，蛇毒測試劑，應探討在適當的個案中使用。

Keywords: Antivenins, enzyme inhibitor, incidence, snake venom

關鍵詞：抗蛇毒血清、酶抑製劑、發生率、蛇毒

Introduction

Snakes all along have been capturing human interest and interacting closely with human culture. They have been a common figure appearing in many religions and rituals. Despite being regarded as owning healing power and used as a symbol in numerous medical profession bodies, to many people they are also a sign of evil and an extremely terrifying venomous creature. In the old tradition of China, snake is one of the deadly five venoms collectively called Wudu. In another longstanding civilized nation Egypt, it is famous for its connection to Cleopetra VII's suicide. In modern era, serious toxicity of snakebites is exemplified by the large number of deaths snakes inflict in South Asia and Africa each year.

Hong Kong is a developed city. The number of snakebites is far less than countries where it is endemic. Despite this, the role and interest of emergency physicians in snakebite management have been increasing in recent years with the development of
toxicology and emergency medicine ward. Akin to the other fields of medicine, the situation of snake envenoming keeps on evolving. The impacts by and the attitudes to the new and potential developments, both in terms of epidemiology and technology, are discussed below.

Incidence

In Hong Kong, the snakebite incidence in the past has never been known with certainty. In 1997, it was estimated to be more than 300 a year. According to the Clinical Data Analysis and Reporting System database of the Hospital Authority, the territory wide number was 124 in 2010. A drop of snakebite incidence is not of surprise if the shrinkage in local agricultural industry is taken into consideration.

Agriculture is a sunset industry in Hong Kong. Of the approximate 1000 km² land area of Hong Kong, only 60 km² are actively farmed including 8 km² for plant farming. Together with aquaculture and forestry, the industry comprised 0.3% of the employment in 2005, and this figure dropped to 0.1% in 2010. Farming is a risk factor of snakebite and contributes to the high snakebite incidence in many countries in South and Southeast Asia. The limbs of the farmers could be bitten during activities such as walking, clearing, weeding and harvesting.

The decline in farming and the ever-growing urbanization no doubt are destroying the living habitats of the snakes, as well as many other wildlife organisms. However, with the continuation of human residing in village house and the maintenance of the present three fourth of the area of Hong Kong as countryside, snakebites will not be historical, although the case number may be smaller in future. To uphold the knowledge of a less common medical problem, constant training is invaluable particularly to those less experienced. Nevertheless, first hand clinical experience is irreplaceable and when necessary, immediate support to the frontline clinicians by the specialists should be in place.

Snakebites may occur outside Hong Kong. Given the increasing movement of Hong Kong citizens across the border, more victims of snakebite in Mainland China may return to our local hospitals for treatment. To date, such reports are sporadic. In light of the fact that the snake species may be different from that in Hong Kong such as Trimeresurus stejnegeri, Agkistrodon halys; knowledge on them has to be equipped.

Venom detection kits

The diagnosis of the correct species causing snakebites is critical because it decides the right antivenom to be administered. Diagnosis is difficult when the snake is not recognised by the victim or not available for examination, or the clinical manifestations are atypical. In regard to this, snake venom detection for species identification is developed in many countries. In Taiwan, an ELISA laboratory test is capable of measuring the venom of the Taiwan cobra at a level of 1 ng/ml. The level of this test correlates with the severity of local tissue destruction and falls after antivenom administration. ELISA technique was also used to provide rapid diagnosis of Naja atra bite at bedside, with result yielded within 20 minutes. The detection limit is 20 ng/ml. In 15 tested subjects, the sensitivity and specificity were 88.9% and 100% respectively. For Crotelus albolabris, the most common snake accounting for the snakebites in Hong Kong, a rapid immunoenzyme kit has been produced in Vietnam for its identification and semi-quantification of its venom in the blood, urine and wound exudates.

Before clinical application of the venom detection assays, adequate trials should be undertook to testify their accuracy and limitation. Local experience should be obtained instead of simple copying of the overseas results as species diversity and similarity are not always predictable. In an Australian venom detection kit, a high false positivity rate has been demonstrated in snakes that are extraordinarily evolutionary separated. Examination of individual toxin groups showed that it was the phospholipase A₂ that displaced considerable cross-reactivity across the species.

The role of the venom detection as a diagnostic tool should be limited to confirmation of clinical suspicion. Patients bitten by confidently identified species, either by means of eye witness or compatible envenoming
features, should be proceeded the next management step and testing for the purpose of objective documentation and ruling out the remote species is not warranted.

Other than guiding the choice of monovalent antivenom, it is far too early to utilise the venom detection results to guide the other aspects of therapy. Although as in the study mentioned above, venom antigenemia declines after antivenom treatment and the level is related to the extent of local tissue injury, their predictability of outcome after treatment remains to be determined. At present, antivenom dosing endpoint can be guided by clinical and laboratory responses. Any extra benefits of venom concentration measurement are unknown. The use of venom detection tests is going to identify more subclinically envenomed victims. In general, administration of antivenoms to them is not recommended.

With respect to research, venom assays may assist the evaluation of the various prehospital first aid methods. Pressure immobilisation with circumferential bandaging retards systemic venom absorption but only works within a defined pressure range that is practically hard to be applied. The Monash and other methods are waiting for more data to assess their efficacy. The venom assays may offer additional means to the others like the radiotracer uptake to measure the extent of reduction of venom uptake into the central circulation.

**Antivenoms**

The current antivenoms used in Hong Kong are monovalent. The correct choice requires prior diagnosis of the specific snake species inflicting the bite but this may be difficult. The Thai Red Cross Society has recently manufactured the polyclonal antivenoms. They are the haemotoxic polyclonal antivenon targeting *Cryptelytrops albolabris*, *Calloselasma rhodostoma* and *Daboia russelii siamensis*, and the neurotoxic polyclonal antivenom to against *Naja kaouthia*, *Ophiophagus hannah*, *Bungarus fasciatus* and *Bungarus candidus*. Other than *Cryptelytrops albolabris*, the lists refer to multiple species rarely involving in our local snakebites. Moreover, systemic neurotoxicity is absent after the bite by our indigenous *Naja atra*, consequently making the use of neurotoxicity identification as an indication of giving the neurotoxic polyclonal antivenom to be unapplicable. Another polyclonal antivenom, which is prepared for *Naja atra* and *Bungarus multicinctus* in Taiwan, is also not ideal to be used in our locality because of the same reason.

Antivenoms have raised a lot of concerns on its safety. In a study in 1990, the green pit viper antivenom we are using locally was reported causing a hypersensitivity rate of 45%. The early reactions of the same antivenom fell to 3.5% in a recent report in 2008. The result difference is in concord with a decrease in allergy incidence over the last four decades in the other countries. To my knowledge, no data on the allergy rate due to the polyclonal antivenoms manufactured by the Thai Red Cross Society have been published. As a reference, the Australian polyclonal snake antivenom causes more frequent reactions than its monovalent components. In regard to the safety of the monovalent green pit viper antivenom, the inclusion of species that are not native to Hong Kong and the additional reactions exhibited by the Australian polyclonal antivenom, the use of the Thai Red Cross Society produced polyclonal antivenoms in Hong Kong is not indicated yet.

**Enzyme inhibitors**

Bites by the viper and the cytotoxic cobra can produce gross local swelling and even necrosis. The local effects are difficult to be controlled by antivenom administered after the bite has occurred. This prompts the research of inhibitors of the components of snake venoms and the inflammatory mediators induced by the venoms that are responsible for the local wound injury. Metalloproteinases, which are present in vipers but virtually absent in *Naja atra*, have been received the greatest attention. They cause direct hydrolysis of proteins in the dermis and at the dermal-epidermal junctions. After prior mixing of a metalloproteinase with its inhibitor batimastat, its pathological effects are completely abrogated. Batimastat is also effective when it is administered early after the toxin inoculation. Another enzyme in vipers and cobras, phospholipase A₂, exhibits a
wide spectrum of toxicity. The myotoxicity it induces can lead to permanent tissue loss, disability and death. Suramin is one of the first therapeutic agents used clinically in the treatment of African trypanosomiasis. Its polyanionic and structurally flexible nature enable it to fit in the cationic phospholipase A2, rendering it inactive in binding to the phospholipid layer of the muscle cell membrane. Significant amelioration of myotoxicity is achieved when suramin is administered soon after local injection of Bothrops asper myotoxin.14 The local toxicity of snake venom is not restricted to the immediate vicinity around the bite mark. It often progresses and the process is facilitated by hyaluronidase. Being a hyaluronidase inhibitor, sodium cromoglycate is effective in reducing the swelling and necrosis ensuing Naja kaouthia and Calloselasma rhodostoma venom injection.15

The promising results of the enzyme inhibitors are yet premature to be transformed to clinical use. They are based on animal studies. The inhibitors were injected within minutes after toxin exposure. Our common venomous snakes, Cryptelytrops albolaris and Naja atra, have not been tested. Further clinically directed evaluations are justified.

**Conclusion**

Snakebites will continue to be a local health issue but may show a trend towards lesser magnitude because of the changing environment. Among the scientific developments discussed, venom detection assay appears relatively ready for our clinical practice. As the assays are derived from overseas snakes, they have to be evaluated against the local species. According to the available data, the Thailand manufactured polyvalent antivenoms seems not adding extra benefits to our currently stocking monoclonal antivenoms. The enzyme inhibitors to mitigate local injury are still being investigational.

**References**

15. Yingprasertchai S, Bunyasrisawat S, Ratanaabangkoon K. Hyaluronidase inhibitors (sodium cromoglycate and sodium aurothiomalate) reduce the local tissue damage and prolong the survival time of mice injected with Naja kaouthia and Calloselasma rhodostoma venoms. Toxicon 2003;42(6):635-46.