

## Snakebite in Indonesia

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### ABSTRAK

Indonesia merupakan salah satu negara tropis dan agraris terbesar di dunia, yang berpotensi memiliki angka kasus gigitan ular yang tinggi namun seringkali tidak tercatat. Pada satu dekade terakhir ini, Badan Kesehatan Dunia (WHO) memasukkan kasus gigitan ular dalam daftar penyakit tropis yang terabaikan. Manifestasi klinis gigitan ular bervariasi bergantung kepada jenis bisa ular berupa gejala ringan hingga mengancam jiwa. Ketepatan pertolongan pertama, serta tatalaksana komprehensif dari setiap kasus gigitan ular diperlukan untuk mengurangi angka kematian dan kesakitan.

**Kata kunci:** gigitan ular, penyakit tropis terabaikan, Indonesia, tatalaksana, serum anti bisa ular.

### ABSTRACT

Indonesia as one of the largest tropical and agricultural countries in the world shared the particularly high burden cases of snakebite. In the last decade, World Health Organization (WHO) has listed snakebite as one of the neglected tropical disease. The clinical manifestations of snakebite could vary according to the type of venoms ranging from mild to life threatening condition. Appropriate first aid treatment and comprehensive management of snakebite cases are warranted to reduce mortality and morbidity rates.

**Key words:** snakebite, neglected tropical disease, Indonesia, treatment, antivenom.

### INTRODUCTION

Indonesia as one of the largest tropical countries in the world had particularly high burden cases of snakebite. In addition, many Indonesians are working in agricultural field which is regarded as high risk population for snakebites.<sup>1</sup> Other neighboring tropical countries in Southeast Asia region such as Malaysia, Thailand, and Myanmar also shared the same burden of disease.<sup>2</sup> Despite that, government and public health community still shared little attention. At the present time in Indonesia, there was no national epidemiology report, lack of national policy on snakebite control program,

and updated national guideline in snakebite management. Limited snakebite information reflects that the disease is still one of the neglected tropical disease in Indonesia. This review aims at summarizing the epidemiology, clinical manifestations, diagnosis, treatment, and prevention strategies of snakebite in Indonesia.

### BURDEN OF DISEASE

In 2009, WHO included snakebites in WHO list of neglected tropical diseases and even until now remains as a global public health problem. Katsusirane et al estimated about 1,200,000–5,500,000 snakebites, 421,000–1,841,000

envenoming, and 20,000-94,000 deaths may occur globally per year, with South Asia and Southeast Asia have the highest burden. In Indonesia, there were 12,739–214,883 snakebite cases estimated with 20–11,581 deaths in 2007.<sup>2</sup> This estimation was mainly based on reported studies and may differ with the actual numbers. There were many factors affecting the accuracy of the reported events, such as many snakebite cases occurred in rural area, traditionally treated, or never managed to reach hospital. Therefore the actual problem of snakebite might be bigger than previously estimated.<sup>3-5</sup>

In Indonesia, no national epidemiological reports are available. Epidemiological data of snakebite cases are very few and derived only from hospital based report. In 1996-1998 there were 180 snakebite cases reported in Hasan Sadikin Public Hospital, Bandung.<sup>6</sup> In Cipto Mangunkusumo National Referral Hospital, there were only forty-two snakebite cases treated between 2004 and 2009. Among them, 17 patients showed envenomation signs.<sup>7</sup> Meanwhile, accurate epidemiological data was required for physicians and health policy maker to educate high risk population, to better distribute antivenom, and to provide prevention control program;<sup>8</sup> while with no accurate data, morbidity and mortality will remain unavoidably high.

#### DISTRIBUTION OF VENOMOUS SNAKES IN INDONESIA

Worldwide, there are about 2,800 species of snakes, but only 320 species are medically important to human and classified into three families of venomous snakes, *Atractaspididae*, *Elapidae*, and *Viperidae*. Colubridae is the largest snake family considered to be harmless among most species, but some severe envenoming cases had been reported.<sup>9,10</sup>

In Indonesia, the distribution of snakebites can be divided into two groups based on biogeographical origins. The first group includes all snake species that have similarity with venomous snakes of Asian origin distributed in West of Wallace's line (Sumatera, Java, Kalimantan, Sulawesi, and the lesser Sunda Island). While the second group has more

similarity with Australo-Papuan region. This region includes East of Wallace's line (West Papua and Maluku).<sup>11,12</sup>

WHO divided snake species into two categories based on its medical importance. The first category includes all highly venomous snakes with the highest medical importance, widely spread, and causing high level of mortality and morbidity. The second category includes venomous snakes which is defined as having secondary medical importance.<sup>12</sup>

Category I of Indonesian venomous snakes distributed in West of Wallace's line consists of Elapidae and Viperidae families. The family Elapidae is represented by *Bungarus candidus*, *Naja sputatrix*, and *Naja sumatrana*.<sup>12</sup> *Bungarus candidus*, also known as Malayan krait/*Ular Weling*, is a nocturnal snake that usually bites at night especially in rural area.<sup>13,14</sup> *Ular Weling* is famous for its lethal dose neurotoxicity (LD50) 3.5 µg per mouse which makes them one of the most toxic snakes.<sup>15</sup> (Figure 1)



Figure 1. *Bungarus candidus*. (Courtesy of David Williams)

The *Naja* species is famous as Ular Kobra in local area and known for their spitting venom ability which is capable of causing venom ophthalmia.<sup>13,16</sup> Cobras can raise their head and spread their hood, as their defense mechanism.<sup>17</sup> (Figure 2)

Viperidae in WHO category 1 consist of *Daboia siamensis*, *Cryptelytrops albolabris*, and *Calloselasma rhodostoma*.<sup>12</sup> Vipers have typically triangular head, laoreal shields, and vertically elliptical pupils.<sup>18</sup> *Cryptelytrops albolabris*/*Ular hijau*/White lipped pit viper live

in tropical forest and bamboo forest<sup>19</sup> and can grow to 1.0 meter in length.

*Daboia siamensis* live in agricultural areas and hide behind the rock crevices and bushes. They are a slow moving nocturnal snake and hiss loudly but can strike fiercely when disturbed.<sup>20</sup> (Figure 3)



Figure 2. *Naja sumatrana*. (Courtesy of David Williams)



Figure 3. *Daboia siamensis*. (Courtesy of David Williams)

*Calloselasma rhodostoma/Ular Tanah/Ular Biludak* is a thick bodied snake that can grow about 1.10 meter in length, with triangular head. This snake is commonly found in lowland forest. *Ular tanah* is not an aggressive snake.<sup>21</sup>

In East of Wallace's line, West Papua and Maluku, the only category I snake is *Acanthopis laevis*.<sup>12</sup> This Elapidae snake is also known as Eastern Death Adder. They live in various

habitats, such as low and highland grass, rainforest, woodland, and savannah. In general, they have short body but can grow up to 1.0 meter in length. They tend to be motionless, but when touched they will strike rapidly.<sup>22</sup> (Figure 4)



Figure 4. *Acanthopis laevis*. (Courtesy of David Williams)

#### CLINICAL MANIFESTATIONS

The clinical manifestations may vary between bites, depending on the type of venom. Envenomings can manifest as local and fatal systemic symptoms, the severity depends on the location of the bite and the amount of venom injected. Pit viper snakebites can produce local manifestation as a local pain, swelling, and local skin necrosis, which in turn can lead to tissue loss and the patient may need to be amputated.<sup>23</sup> The effect of cytotoxic and myotoxic of the venom can lead to rhabdomyolysis and in the end lead to acute renal failure.<sup>4</sup> Crotaline venom mainly damaged the endothelial cell, causing plasma leakage and may lead to hypovolemic shock.<sup>24</sup>

Cobra, Kraits (*Bungarus spp.*), and sea snakes are known for their neurotoxicity feature.<sup>25</sup> Neurotoxin can exert effect at pre-synapse and post-synapse. Pre-synaptic toxins such as beta-bungarotoxin (b-BuTX) lead to degeneration of motor nerve, depletion of synaptic vessels, and destruction of motor nerve terminals; while post-synaptic neurotoxins such as alpha-neurotoxins bind to the acetylcholine receptor and lead to neuromuscular blockade.<sup>26</sup> The cranial nerves are usually affected first. Acute neuromuscular paralysis such as ptosis, facial weakness, paralysis, and respiratory muscle weakness are commonly reported.<sup>27</sup>

Bleeding manifestations are reported for Rhabdophis snakebite and Crotaline. The fatal case is reported as bilateral acute epidural hemorrhage and subcortical hemorrhage with cerebral herniation.<sup>28</sup> Other manifestations are ecchymosis, hematemesis, melena, and hematuria.<sup>24</sup> These bleeding manifestations are mainly caused by venom-induced consumption coagulopathy (VICC) and thrombocytopenia.<sup>29,30</sup> VICC occurred because of serine protease and procoagulant enzyme acting as factor V activators, factor X activators, prothrombin activators, and thrombin-like enzymes (TLEs), leading to a vicious cycle which involved fibrin formation and degradation by plasmin, which in turn results in depletion of coagulation factor.<sup>12,29,31</sup>

## DIAGNOSIS

Snakebite is basically a clinical diagnosis and confirmed a history of bites by the patient or family or a witness. Four important questions should be asked when evaluating the patient: the location of the bite, the time patient got bitten, the characteristics of the snake, and the symptom.<sup>9,24</sup> Identification of snake species should be done even though sometimes it can be difficult by anamnesis alone. Venomous snakes are usually characterized by triangular heads, heat sensing pits, elliptical pupils, single row of subcaudal scales, and has typical bite mark with only one or two fangs punctures on the skin. Whereas non-venomous snakes are characterized by round head, round pupil, double row of ventral scales, and the bite mark displays small punctures in rows.<sup>32,33</sup>

Physical examination should be focused on vital signs, bleeding manifestation, bite site including bite marks, bruising, and draining lymph nodes. Neurological examination must be performed including cranial nerves, motor, and sensory examination.<sup>26</sup>

Required laboratory investigations are generally complete blood count, electrolyte, creatinine, BUN, clotting time, bleeding time, prothrombin time, aPTT, fibrinogen level, D-dimer, AST, ALT, creatine kinase, and blood type.<sup>10,34</sup>

SEARO recommends a 20-minute whole blood clotting test (20WBCT). The 20WBCT is a useful test for developing countries such as Indonesia, because snakebites can occur in rural areas where primary health care facilities do not have capability to perform extensive clotting tests. This test can be done on bedside and yields fast results. The test was done by pouring 2 mL of fresh venous blood in a dry glass vessel, and left it for 20 minutes. If the blood is still unclotted then the patient may have VICC. It can be used as a clue for viper bite and rules out elapid bite, also monitoring the effect of antivenom in terms of VICC treatment.<sup>12</sup>

Other routine tests that should be done are ECG and urinalysis to check for glucosuria, proteinuria, and myoglobinuria.<sup>12</sup>

## SNAKEBITE MANAGEMENT

Management of snakebite requires comprehensive and collaborative approaches from pre-hospital to advanced management in hospital. Even though there are already many published guidelines, the implementation is quite hard especially in rural areas. Delay in patient transport, improper first aid management, initial visit to traditional healer, and limited antivenom supply are some of the factors to the worsening of poor clinical outcome.<sup>35-37</sup> In Indonesia, available guideline on snakebite management was published by *Sentra Informasi Keracunan Nasional Badan POM*.<sup>38</sup>

### First Aid

Proper first aid management became clinically important to be done, as it affected the outcome of patients.<sup>39</sup> First aid management should be given as soon as possible by the nearby person with proper procedure, followed by transportation to hospital, possibly along with the snake. One of the most well-studied first aid procedures is pressure bandage with immobilization (PBI) recommended by Australian authorities. Elastic broad bandage (15 cm) is applied at the bite site and covering the whole limb with the same pressure for sprained ankle.<sup>34</sup> The rationale of this technique is blocking lymphatic flow without compromising arterial or venous blood flow,

therefore can limit the venom spreading.<sup>40</sup>

Many traditional first aid managements should not be done anymore as it is potentially harmful. Making incisions, and rubbing at the site of the bite wound could promote venom absorption. Electric shock, applying harmful herbal remedy, tying tight tourniquet and sucking out venom with mouth are not recommended.<sup>9,41</sup>

### In-hospital Management

Initial management at hospital following primary surveys is recommended by Advanced Trauma Life. Support guidance involves securing airway, breathing and circulation. Every patients needs to be observed for hemodynamic changes and signs of envenomation. Patients need to be reassured to decrease their anxiety, as the data show most of snakebites are caused by nonvenomous species and about half of venomous snakebites occurred with no venom released.<sup>33</sup> Paracetamol and opioid could be given as pain reliever, while NSAID are generally not recommended because of bleeding risk. In vomiting patient, recovery position with head turned to one side should be done to prevent aspiration and the patient can be given chlorpromazine 25-50 mg.<sup>9</sup> Routine tetanus prophylaxis is also recommended to be given for snakebite victims.<sup>38</sup>

*Sentra Informasi Keracunan Nasional Badan POM* recommends routine administration of antibiotic prophylaxis.<sup>38</sup> A study in Taiwan found that gram negative bacteria, such as *Morganella morganii*, *Aeromonas hydrophila* and *Enterococcus* was the common pathogen responsible for wound infection following snakebite. They recommended the use of piperacillin/tazobactam, quinolone, second- or third-generation cephalosporin for empirical therapy.<sup>42</sup> While, Garg et al<sup>43</sup> found that Gram positive bacteria, such as *Staphylococcus aureus* was the most common pathogen, followed by Gram negative bacteria *Escherichia coli*. Ciprofloxacin was recommended as empiric therapy due to gram positive and negative coverage.

### Antivenom

Antivenom is the only definite therapy in snake envenomation but there were some

limitations in its usage such as hypersensitivity reaction and not readily available.<sup>9</sup> According to SEARO guideline, indications for antivenom are hemostatic abnormality, neurotoxic signs, cardiovascular abnormalities, acute kidney injury, hemoglobinuria, myoglobinuria, local swelling more than half of the bitten limb within 48 hours of the bite, rapid extension of swelling, and enlarged tender lymph node.<sup>12</sup>

Antivenom should be given immediately whenever clinically indicated, however this practice is not always visible to do because of the limited availability of antivenom and the difficulty to identify the snake.<sup>44</sup> Delayed anti-venom administration was reported still successfully treating the envenomings, therefore antivenom should be given as long as indicated.<sup>45</sup>

In Indonesia, the only snake antivenom available was Biosave®, produced by Biofarma, which was made from Equine serum. Biosave® is a polyvalent antivenom and indicated for neurotoxin produced by *Naja sputatrix*, *Bungarus fasciatus*, and hematoxin produced by *Agkistrodon rhodostoma*. For the first dose, 2 vial @5 ml was diluted with normal saline to achieve concentration of 2%, then infused with a rate of 40-80 drops per minute. Another dose could be given 6 hours later. If the envenoming symptoms still persist, antivenom could be given every 24 hours with the maximal dose of 80-100 ml. Undiluted antivenom could be given by very slowly pushing intravenous. Allergic test must be done before administration and monitoring must be done during and post administration. This polyvalent was not effective to neutralize venoms produced by snake from East Indonesia such as *Acanthopis antarticus*, *Xyuranus scutellatus*, *Pseudechis papuanus*, also *Enhydrina cystsa*, due to no cross-neutralization ability.<sup>12,46</sup>

In VICC patient, antivenom was the mainstay treatment. Antivenom would bind to toxin, make it inactive, and promote elimination. However, there were some cases where antivenom failed to give improvement in VICC and recurrent coagulopathy. Experts believed the failure of antivenom for VICC treatment was caused by the rapid toxin effect, as once the coagulation pathway activated it was irreversible. However, antivenom was still useful in these cases because

it bind to procoagulation toxin and give time for coagulation factor to recover. Therefore, in terms of VICC, antivenom should be administered early.<sup>29,47,48</sup>

In case of severe bleeding, the patient may need coagulation factor replacement, such as fresh frozen plasma, cryoprecipitate, or whole blood transfusion. A study conducted in Australia reported that administration of FFP after antivenom was given would help replenish coagulation factor.<sup>47,48</sup> The use of heparin for VICC was not supported by sufficient evidence and controversial due to mixed result. Therefore, the use of heparin was not recommended by WHO.<sup>12</sup>

In management of neurotoxicity, early administration of antivenom was critical because antivenom was unable to neutralize after venom bind.<sup>26</sup> Early intubation may be needed to secure the airway in patient with bulbar involvement.<sup>49</sup> Trial of cholinesterase may be useful and should be given whenever neurotoxic symptoms were evident. Since edrophonium was not available in Indonesia, a longer-acting neostigmine could be given intramuscularly 0.02 mg/kg for adult. Atropine could be given as premedication to minimize adverse effect from neostigmine administration.<sup>18,26,49,50</sup>

As reported, the mortality rate of snake bite inducing acute renal failure is 15% to 20%.<sup>51,52</sup> Therefore, evaluation of any acute renal failure signs such as oliguria, hematuria, proteinuria was important. So the patient can be treated earlier and referred to center with dialysis facility. Antivenom should be given early and renal replacement should be initiated as soon as indicated. Peritoneal dialysis was reported having the ability to reduce the mortality of acute renal failure following snake bite.<sup>53,54</sup> Acidosis and hyperkalemia, should be treated accordingly. Furosemide challenge could be given to improve urine output. Sodium bicarbonate and mannitol could be used to prevent renal damage caused by myoglobinuria, however their use should be avoided in patient with established acute renal failure due to hyperosmolarity and hypervolemic effect.<sup>12,53</sup>

Early detection of compartment syndrome was important. Diagnosis could be made by combining

intracompartmental pressure measurement and symptom based such as severe pain and pain with passive stretch. Antivenom should be administered, as it can reduce tissue pressures and myonecrosis. Fasciotomy was not the first line treatment, and only indicated if there was no improvement after antivenom administration. However, prophylactic fasciotomy were generally not recommended.<sup>12,55</sup>

## PREVENTION

Prevention of snakebite becomes an important strategy to reduce the number of fatal or complicated cases. Prevention can be done by giving education to high risk population about local venomous snake species, snake's habits, and some strategies to avoid snakebites. Some avoidance strategies are avoiding potential snake's habitat such as tall grass, bushes, swamps, and holes in the ground; wearing loose, long pants, and boots especially for agricultural workers; using flashlight when walking during the night. However, in Indonesia all the information above might not be well distributed.<sup>12,56</sup>

## CONCLUSION

Snakebite is a potentially important public health problem in Indonesia, but lacking detailed information on disease burden. Therefore health care providers are warranted to have knowledge in snake identification, proper first aid treatment, and case management in referral setting; as well as to involve the high-risk population in the prevention program.

## CONFLICT OF INTEREST

The authors affirm no conflict of interest in this paper.

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