

Clinical Practice Guideline : Management of venomous snake bites

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หน่วยปฏิบัติการวิจัยค้ำานพิษงูและงูพิษกัด

คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

Venomous snakes of Thailand

■ Elapid snakes: Neurotoxin

- ◆ Cobra งูเห่า: Cobrotoxin
- ◆ King Cobra งูจงอาง: ?
- ◆ Krait งูสามเหลี่ยม และ งูทับสมิงคลา: Bungarotoxin

■ Viper snakes: Hematotoxin

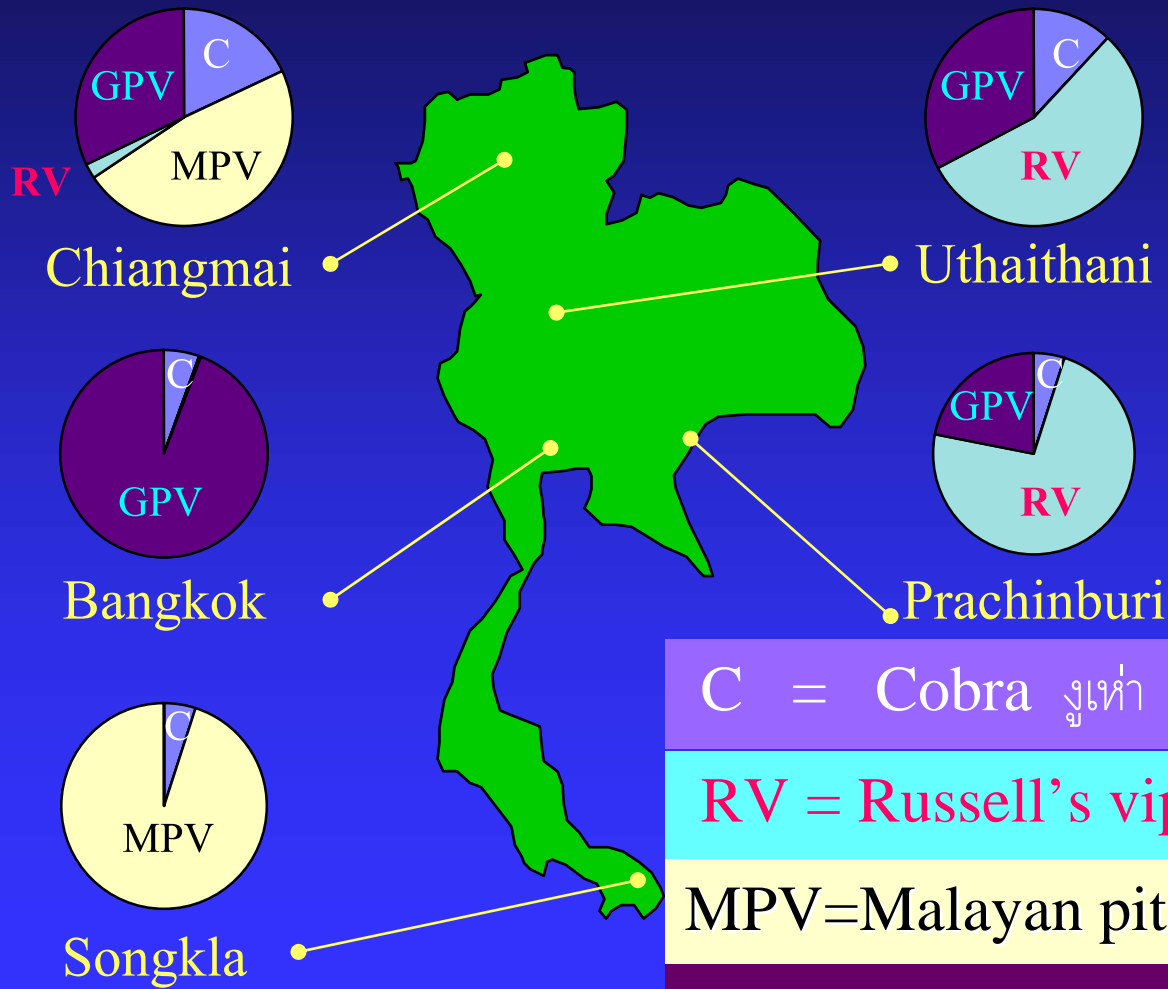
- ◆ Russell's viper งูแมวเซา: Hematotoxin and nephrotoxin
- ◆ Malayan pit viper งูกะปะ: Hematotoxin
- ◆ Green pit viper งูเขียวหางไหม้: Hematotoxin

■ Sea snakes: Myotoxin

Venom = a mixture of toxins



Epidemiology of snake bites



C = Cobra งูเห่า

RV = Russell's viper งูแมวเซา

MPV = Malayan pit viper งูกะปะ

GPV = Green pit viper งูเขียวหางไหม้

Management of venomous snake bites

■ Management of systemic envenoming

- ◆ Cobra envenoming
- ◆ Russell's viper envenoming
- ◆ Malayan pit viper envenoming
- ◆ Green pit viper envenoming

■ Preventing adverse reactions from antivenom

■ Management of snake bite wounds

- ◆ Reduction of edema
- ◆ Microbiology of snake bite wounds
- ◆ Role of Tetanus prophylaxis
- ◆ Role of Prophylactic antibiotics
- ◆ Role of Steroids

Cobra งูเห่า

■ *Naja* sp.

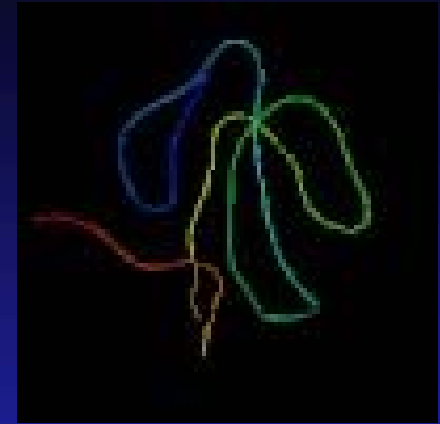
- ◆ งูเห่าไทย: *Naja Kaouthia*
- ◆ งูเห่าพ่นพิษ: *Naja Siamensis*

■ Small fangs

■ Highest case fatality of all venomous snake bites



Cobra venom พิษงูเห่า



■ Alpha-neurotoxins:

◆ Small proteins:

- ◆ Short toxins: 61 amino acids 4 disulfide bonds
- ◆ Long toxins: 131 amino acids

◆ A post-synaptic toxin

- ◆ neuromuscular junction blockade

■ Reversible by edrophonium (Tensilon®)

◆ Acetyl cholinesterase

- www.ionchannels.org/structure.php?start=240

Symptoms of cobra envenoming



Neuromuscular junction blockade

- ptosis
- drooling
- dysphagia --> aspiration
- ventilatory failure
- generalized paralysis

Not all bites result in envenoming [Dry bites]

Management of cobra bites

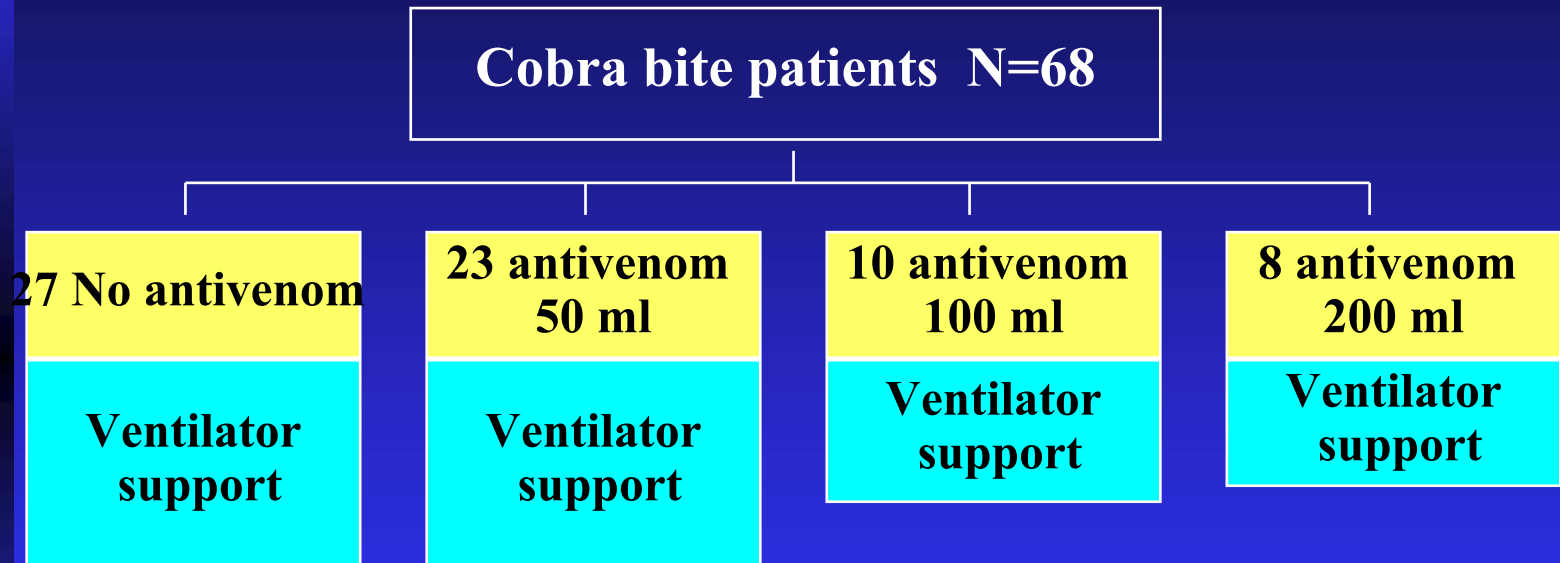
■ Systemic envenoming

- ◆ Role of Edrophonium (Tensilon)
- ◆ Role of antivenom
- ◆ Dosage of antivenom
- ◆ Assisted ventilatory support

■ Local wound care

- ◆ Infectious complications

Cobra bites: Optimal dose of antivenom



- Thai cobra antivenom made by Queen Saowabha Memorial Institute (สถาบันเสาวภา)
- A controlled trial
- antivenom reduce duration of assisted ventilation

Antivenom (Neurotoxin)

- Could not prevent the progression of muscle weakness to respiratory failure
- However, antivenom significantly shortened the duration of assisted ventilation (10 vs 44 hours)
- Single bolus dose is preferable
- 100 ml. for cobra and 50 - 100 ml. for king cobra and banded krait

Cobra bites: Other therapies

■ Steroid IV is not effective

- ◆ 5 cases of Cobra bite, Dexamethasone 10 mg IVq30min x 4 before cobra antivenom, No response (Trisnananda *et al* (1978), Southeast Asian J Trop Med Publ Hlth 9:71-3).

■ Ventilatory support alone is effective

- ◆ 4 cases of Cobra bites,
- ◆ Assisted ventilation started when hypoventilation is evident
- ◆ Median time of support =
- ◆ (Pochanukul *et al* (1994), J Med Assoc Thai 77:161-4)

Malayan krait

งูทับสมิงคลา

- *Bungarus candidus*
- Nocturnal snake หากินกลางคืน
- Painless bite กัดไม่เจ็บ
- Highest cause of mortality from snake bite
 - ◆ No antivenom until recently



Malayan krait toxins

■ Beta-bungarotoxins:

- ◆ A Phospholipase A2

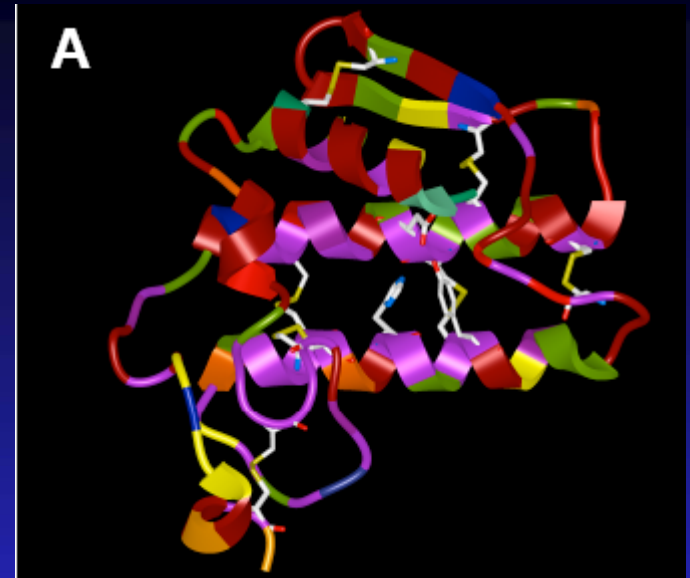
- ◆ **A pre-synaptic toxin**

 - ◆ Permanently damage axon

■ NOT Reversible by edrophonium

- ◆ Recovery by regeneration of axon

- www.ionchannels.org/structure.php?start=240



Malayan krait antivenom

- May partially reverse neurotoxicity
- Or may not work at all
- Regimen is not established

Russell's viper

ឡាសេវា

- *Daboia russelli siamensis*
- Prevalent in Central Thailand, Myanmar, India, Sri Lanka
- Long flexible fang
- Russell's viper venom (RVV) activate Factor X directly

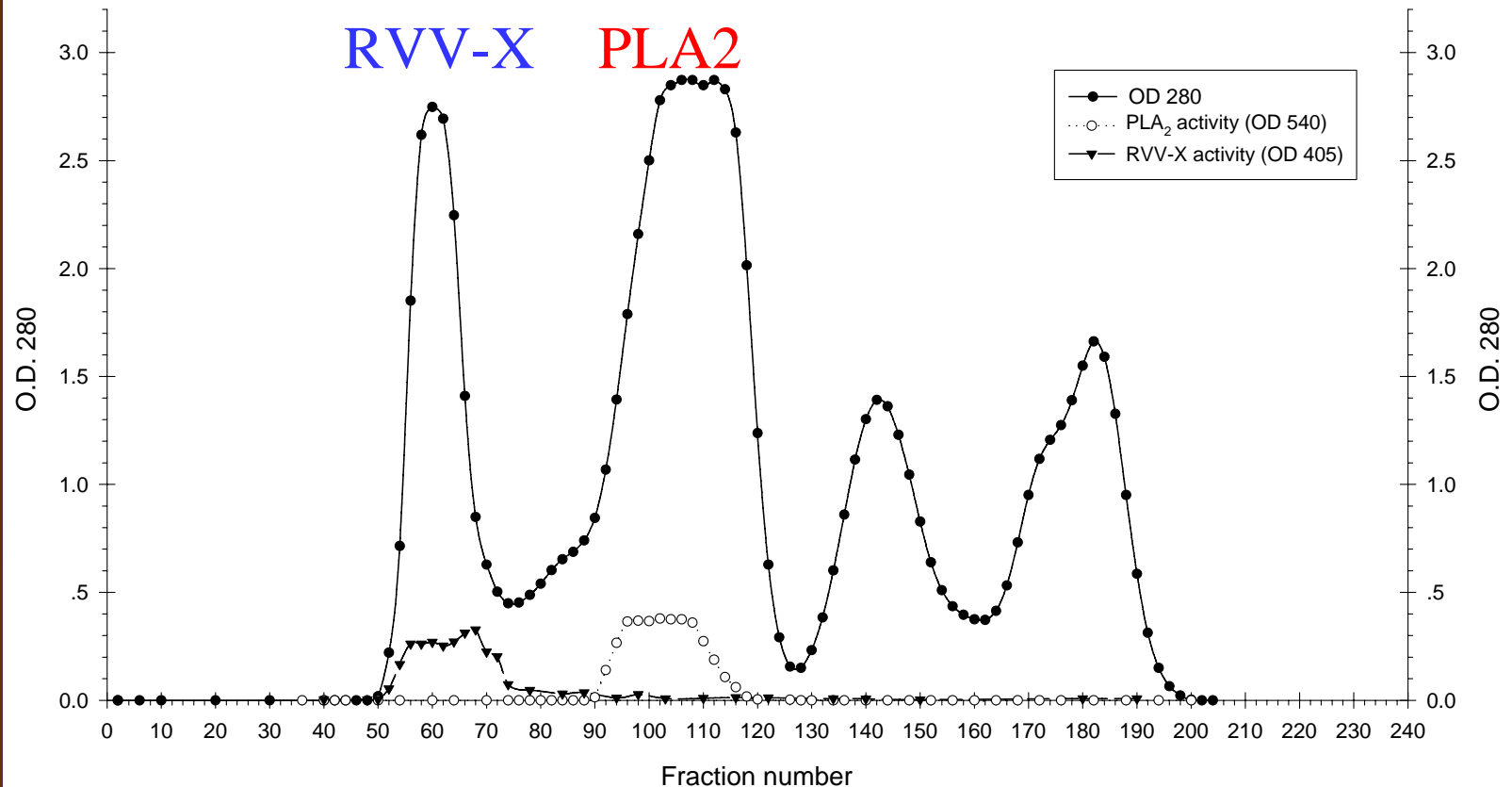


The chromatographic profile of crude RVV on Sephadex G-100 column

RVV 400 mg in 0.05 M Tris-H₃PO₄ + 1 mM benzamidine-HCl, pH 7.5

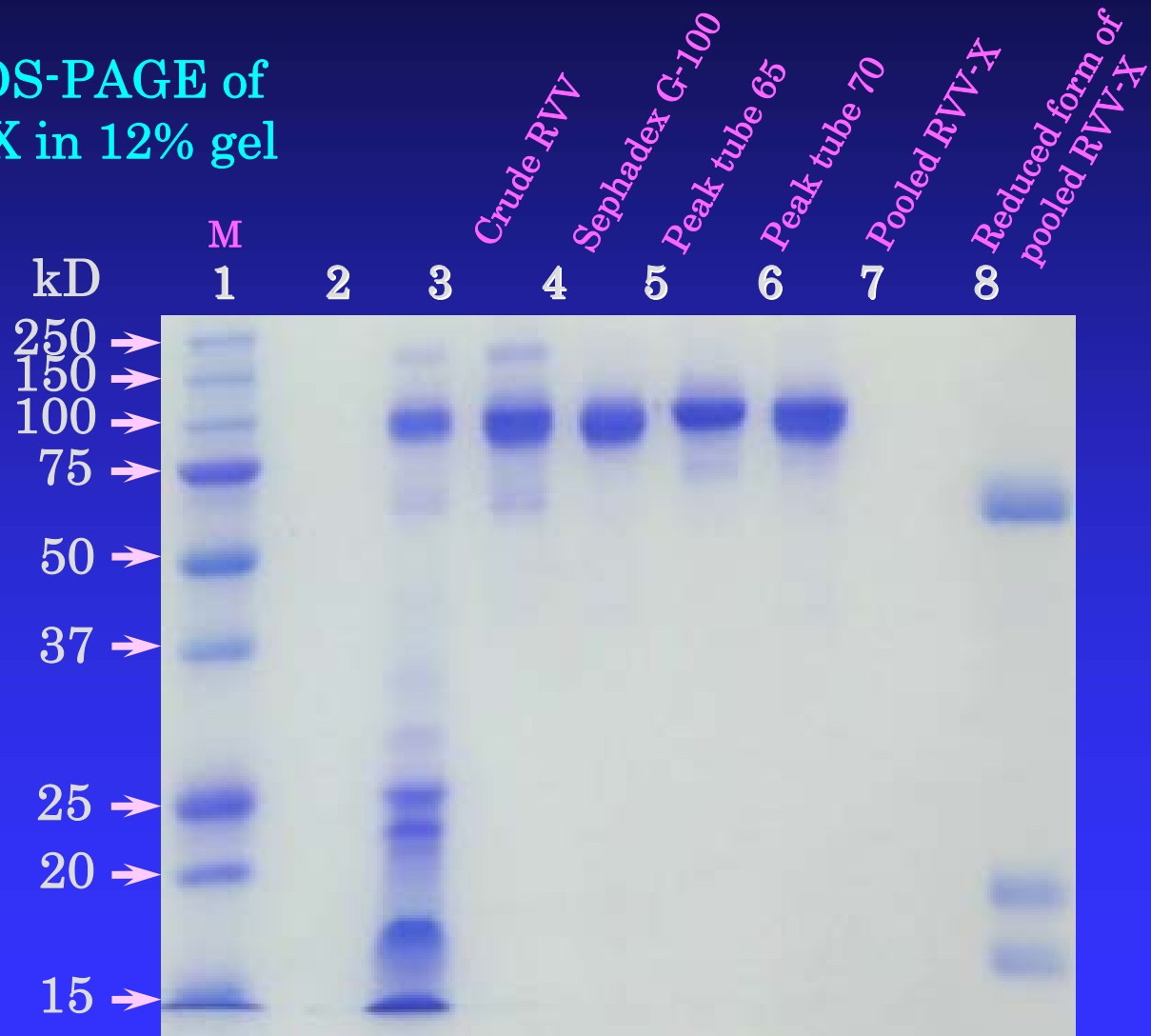
column size : 22/7 x (1.3)² x 70 = 370 ml
fraction size : 2 ml/tube
sample size : 4.149 ml in 0.05M Tris-H₃PO₄ + 1 mM Benzamidine-HCl, pH 7.5
running buffer : 0.05M Tris-H₃PO₄ + 1 mM Benzamidine-HCl, pH 7.5
conc. sample 400 mg
PLA₂ (sample 1:100) & RVV-X activity (sample 1:80)

flow rate : 10 ml/hr

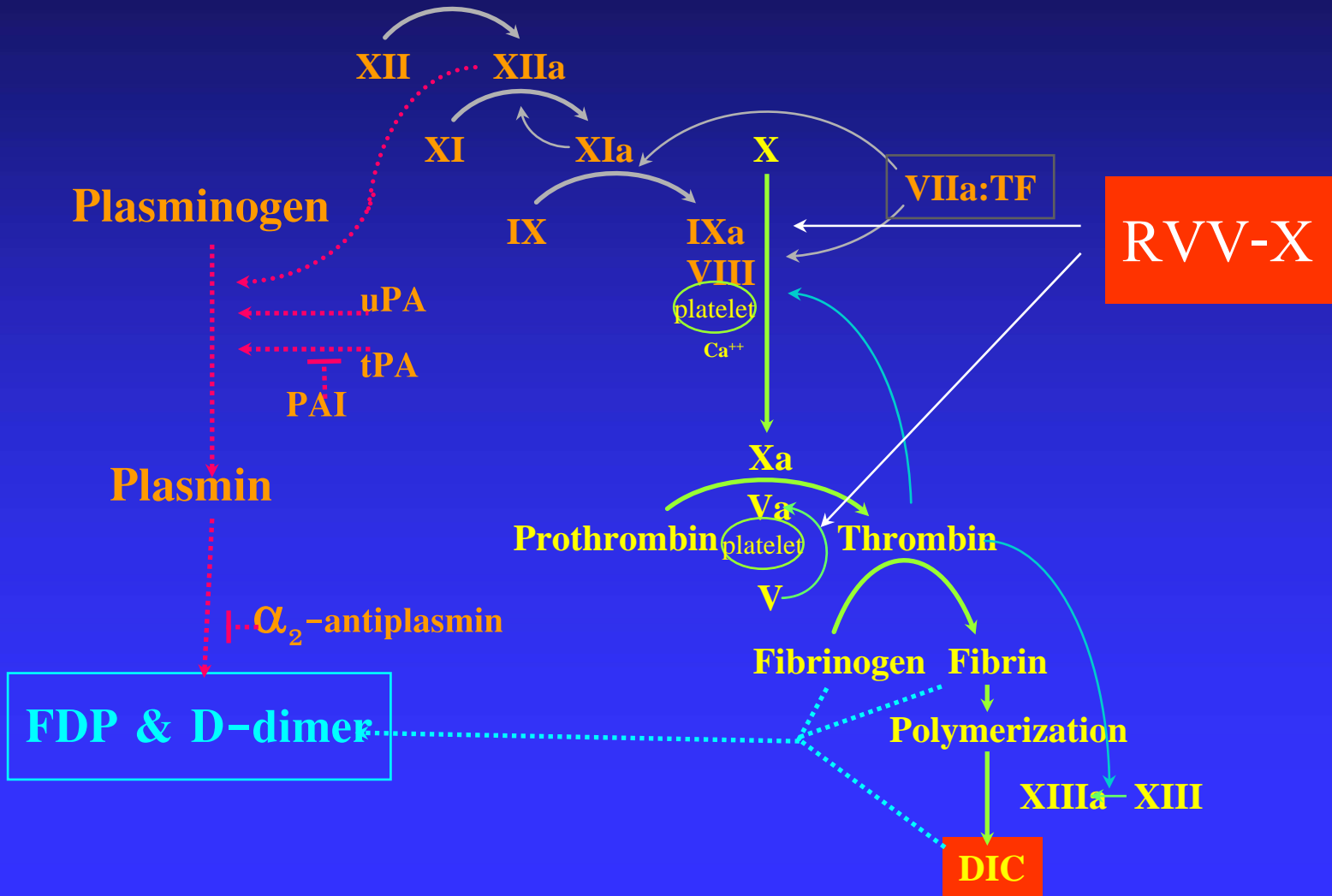


RV venom

An SDS-PAGE of
RVV-X in 12% gel



RVV: Mechanism of Action



Purified RVV-X activates clot in A hemophilia patient with FVIII inhibitor

plasma	Venous Clotting Time (min)	
	w ithout RVV-X	w ith 200 ng RVV-X
normal plasma	14.5	2.0
hemophilia A plasma	260.0	2.0



*Clotting time in normal plasma is 10-15 min.

Most abundant transcripts found in *Daboia russellii siamensis* venom

Putative proteins (or gene*)	No. clones
Phospholipase A2 (PLA ₂)	17 (12.6%)
BPP-CNP precursor homolog*	5 (3.7%)
→ Coagulation factor X activator (RVV-X)	3 (2.2%)
Coagulation factor V activator (RVV-V)	2 (1.5%)
Kininreleasing and fibrinogen-clotting serine proteinase ₂	2 (1.5%)
Nucleotidase	2 (1.5%)
Dendritic cell protein	2 (1.5%)
Tyrosine phosphatase	2 (1.5%)
NADH dehydrogenase subunit I	2 (1.5%)

Total of 135

Russell's Viper bites

งูแมวเซากัด

- Local pain, swelling and bleeding from bitten site
- Laboratory evidence of DIC
 - ◆ Venous clotting time (VCT)
 - ◆ Thrombocytopenia
- Acute Renal failure

Geographical variation in the Clinical manifestations of *Daboia russellii* bite.

	<u>Sri Lanka</u>	<u>India</u>	<u>Burma</u>	<u>Thailand</u>	<u>Taiw</u>
Coagulopathy		+		++	++
Renal failure	++	+		++	+
Pituitary infarction	-		+	++	-
Intravascular haemolysis	++	+		-	+
Neuro-myotoxicity	++	+		-	-
Generalized capillary permeability	-	-		++	-
Primary shock/hypotension	-		+	++	

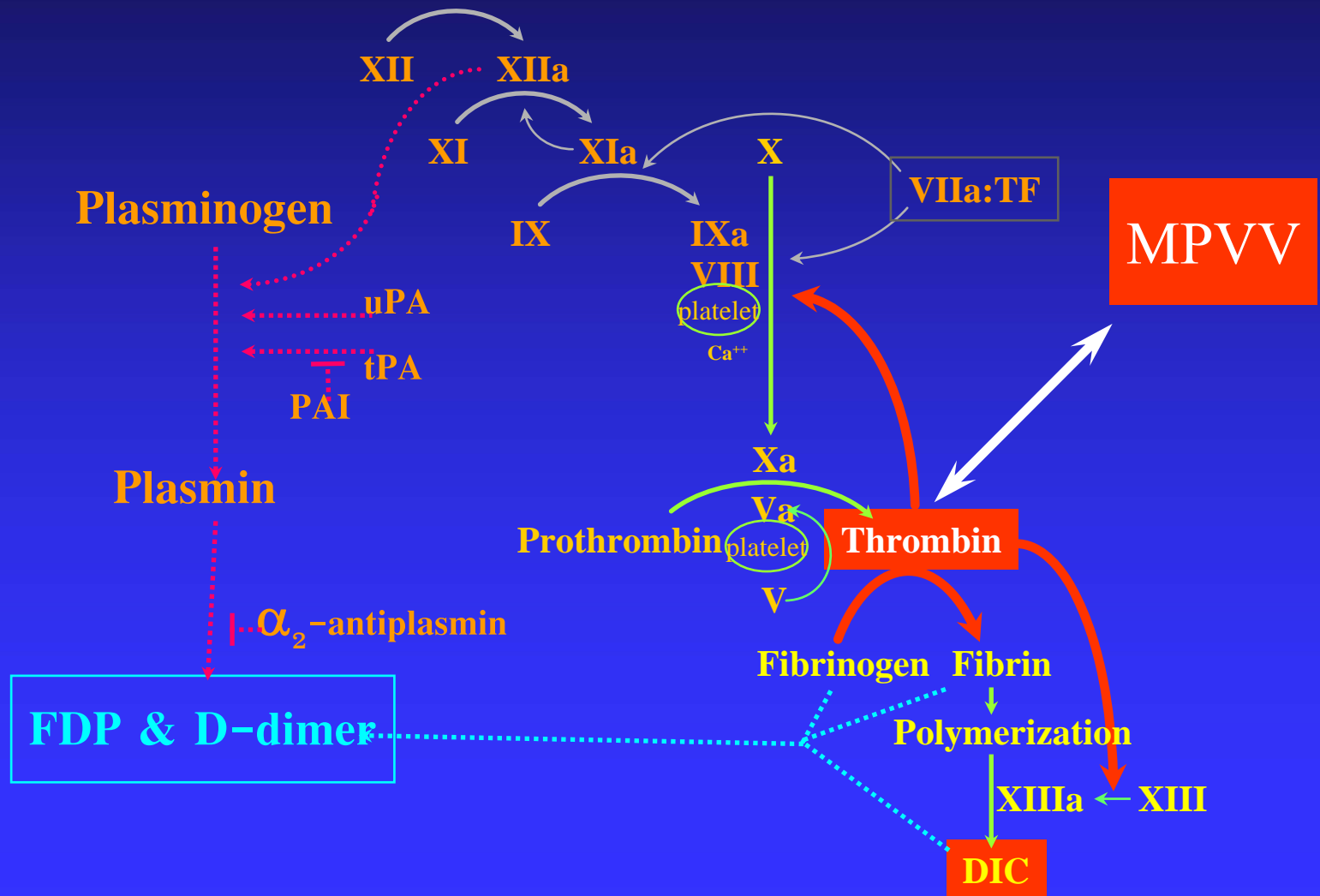
Malayan pit viper

งูกะปะ

- *Calloselasma*
Rhodostoma
- Found throughout Thailand but most prevalent in Southern Thailand, Malaysia.
- Long flexible fang
- Malayan pit viper (MPV) venom (**ancrod**) has **thrombin-like** activity



MPV venom: Mechanism of Action

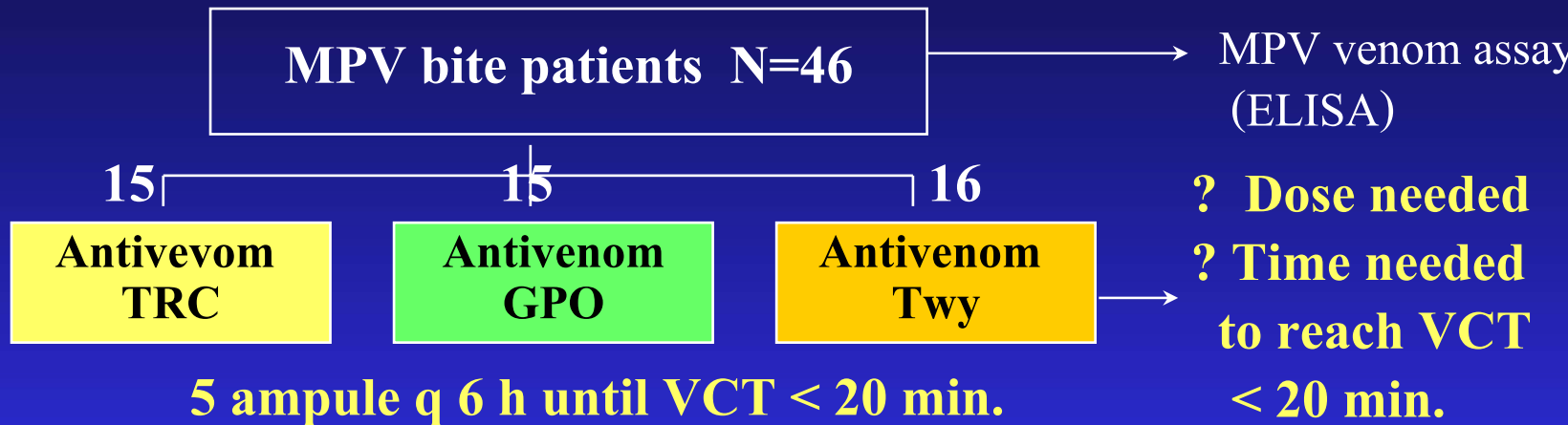


Malayan Pit Viper bites

งูทะเลกัด

- Local pain, swelling and bleeding from bitten site
- Death is rare, but extensive necrosis is common.
- Laboratory evidence of DIC
 - ◆ Venous clotting time (VCT)
 - ◆ Thrombocytopenia
- **MPV antivenom** is most important
 - ◆ What preparation of antivenom?

MPV bites: Role of antivenom



- Trang, mono-specific MPV antivenom made by **Thai Red Cross (TRC)**, **Government Pharmaceutical Organization (GPO, องค์การเภสัชกรรม)**, or **Twyford Pharmaceutical (Twy)**
- Randomized, controlled trial (unblinded)
- **GPO MPV-Antivenom and Twy were superior than TRC.**

MPV bites: Dose of antivenom

MPV bite patients N=139
VCT abnormal=64

↓
antivenom
GPO

Dose needed	None	5	10	15	25
Children N=29	17	6	4	1	1
Adult N=139	75	37	19	6	2

5 ampule q 6 h until VCT < 20 min.

- Trang, MPV antivenom from **GPO (องค์การเภสัชกรรม)**
- Single-arm study, No comparison
- No death, Correction of VCT achieved in 6-18 hours.
- Allergic reaction =12 in 64 (20 %)
- **Dose of MPV-Antivenom needed were similar in children and adult.**

Wongwanich and Yoksarn (1985) Bull Dep Med Serv 10:783-8.

Green pit viper

งูเขียวหางไหม้

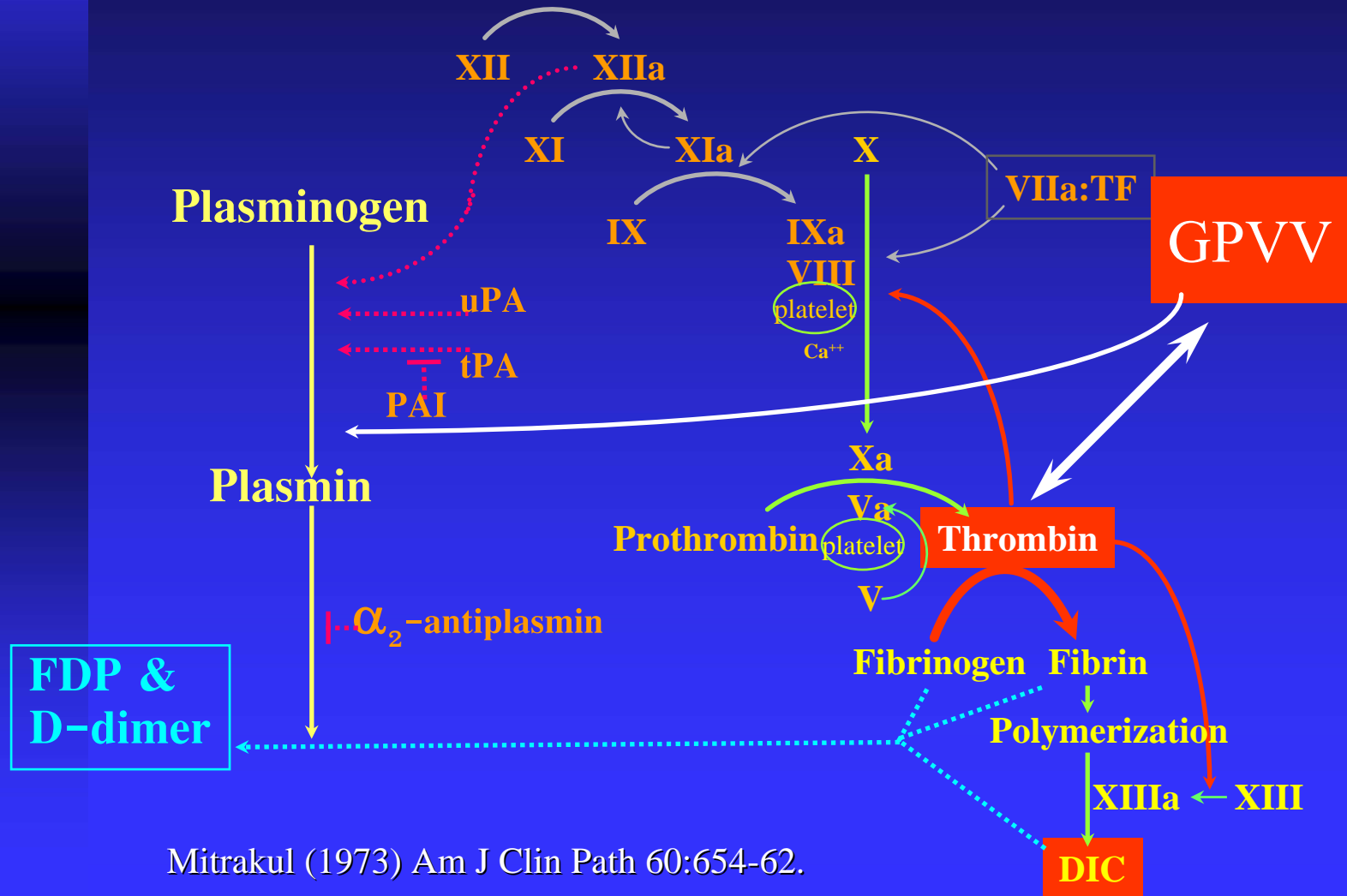
■ *Cryptelytrops* sp.

- ◆ *C. albolabris*
- ◆ *C. macrops*
- ◆ *C. popeorum*
- ◆ *C. erythrurus*



- Found throughout Thailand but most prevalent in Central Thailand
- Long flexible fang
- Green pit viper (**GPV**) venom has **thrombin-like** activity

GPV venom: Mechanism of Action



Mitrakul (1973) Am J Clin Path 60:654-62.

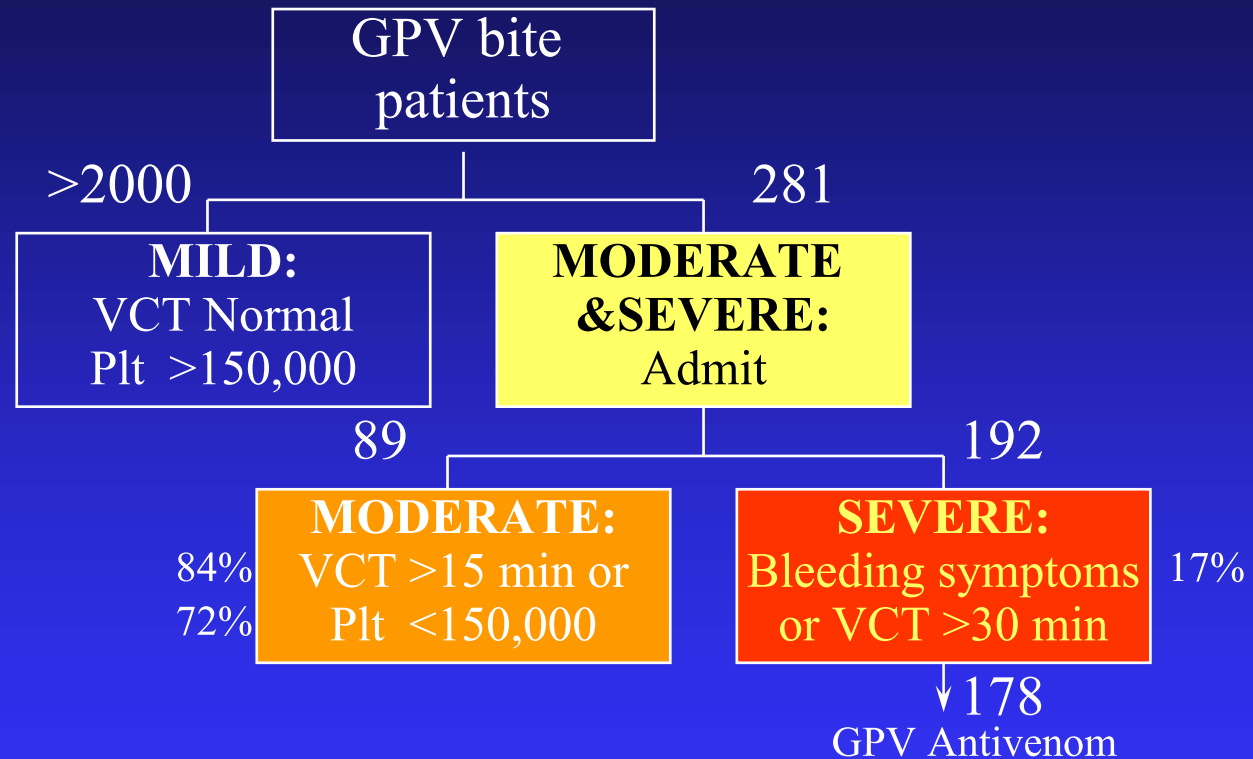
Green Pit Viper bites งูเขียวหางไหม้กัด

- Local pain, swelling and bleeding from bitten site
- Death is rare,
- **Laboratory** evidence of Fibrinolysis
 - ◆ Venous clotting time (VCT) prolonged
 - ◆ Hypofibrinogenemia (Normal F V, VII, VIII, IX, X)
 - ◆ Thrombocytopenia
- **Untreated patients:** platelet count, fibrinogen level becomes normal in 2 weeks,
- **GPV antivenom** result in prompt resolution of coagulopathy

Management of GPV bites

- No **clinical trials** exist on the use of GPV antivenom
- **Antivenom is indicated** when
 - ◆ patients has systemic bleeding
 - ◆ markedly prolonged VCT (>30 min)
- It is **controversial** whether antivenom should be given if VCT is prolonged, thrombocytopenia, or both.

Management of GPV bites



- Chulalongkorn Hospital (Medicine)
- The only predictor for bleeding is : VCT>15m + Plt<150K
 - ◆ Odds ratio = 3.6

Rojnukarin *et al* (1996) Thai J Hematol Transfus.

Adverse Reactions to GPV-AV: Anaphylactoid reactions

- **Skin test** with GPV antivenom +ve in 9%
 - ◆ 1:100 dilution, 0.02ml intradermally
 - ◆ +ve = wheal >5mm at 15 minutes
 - ◆ If **skin test +ve**, no desensitization: 3/4 symptomatic
 - ◆ If **skin test +ve** , given desensitization: 2/2 no symptom
- **Risk of adverse reaction** with antivenom = 20%
 - ◆ The risk with purified antivenom = 10%
 - ◆ Anaphylactic shock (2%), bronchospasm (3%)
 - ◆ Even if **skin test -ve**, anaphylactoid reactions still occurs

An approach to snake bite at C.U.

Unknown Venomous
Snake bite, swollen limb

CBC, VCT

An approach to snake bite at C.U.

Unknown Venomous
Snake bite, swollen limb

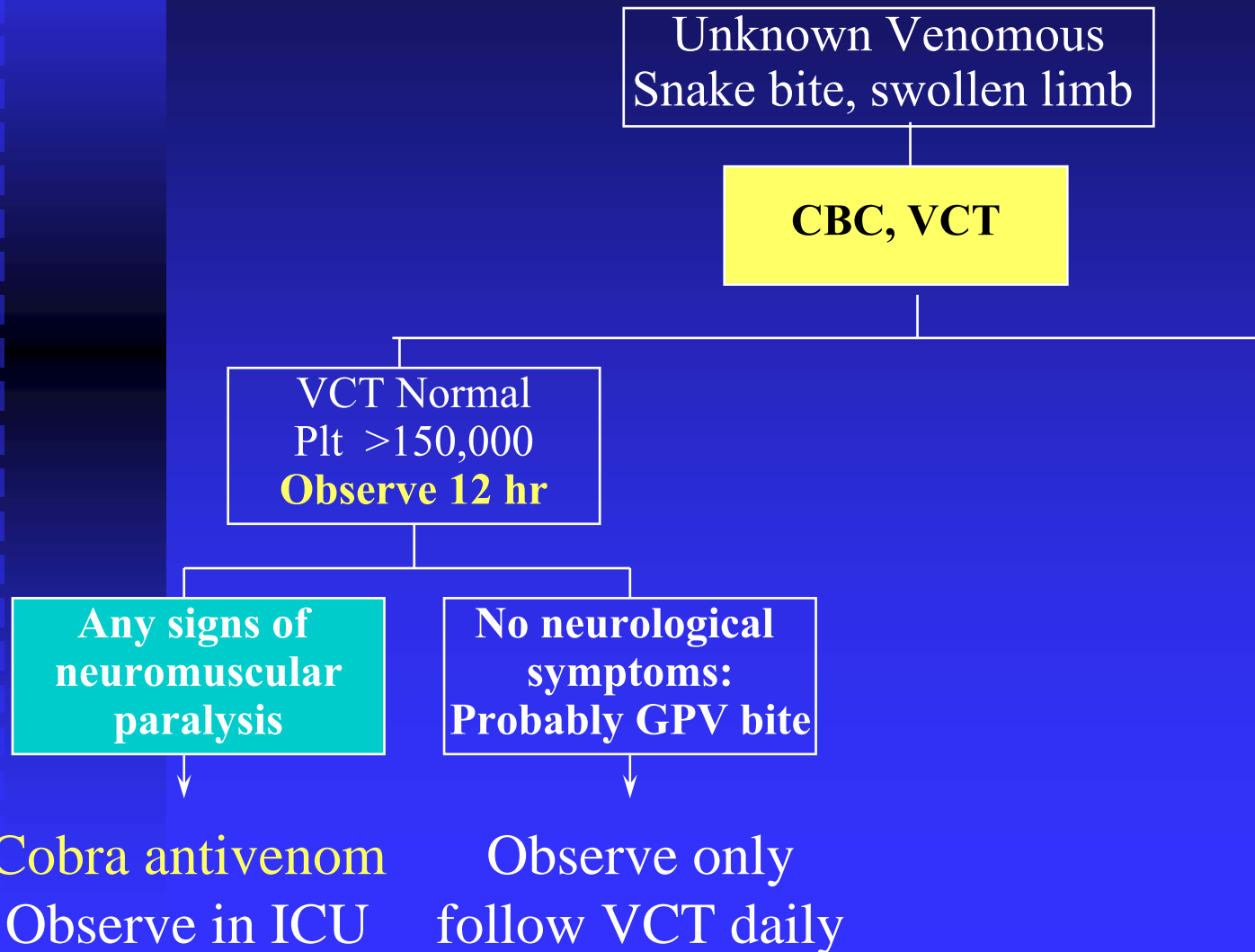
CBC, VCT

VCT Normal
Plt >150,000
Observe 12 hr

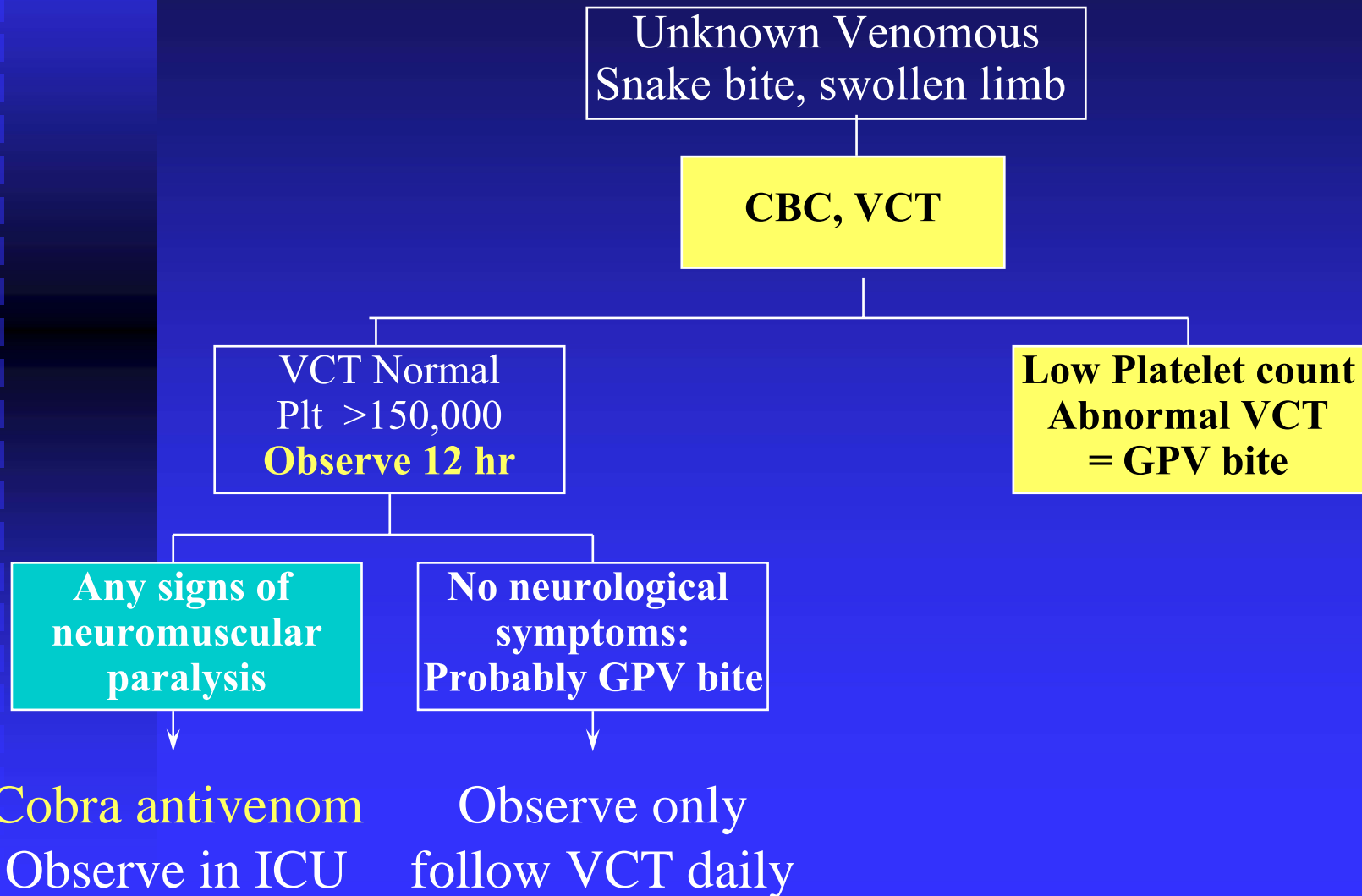
**Any signs of
neuromuscular
paralysis**

Cobra antivenom
Observe in ICU

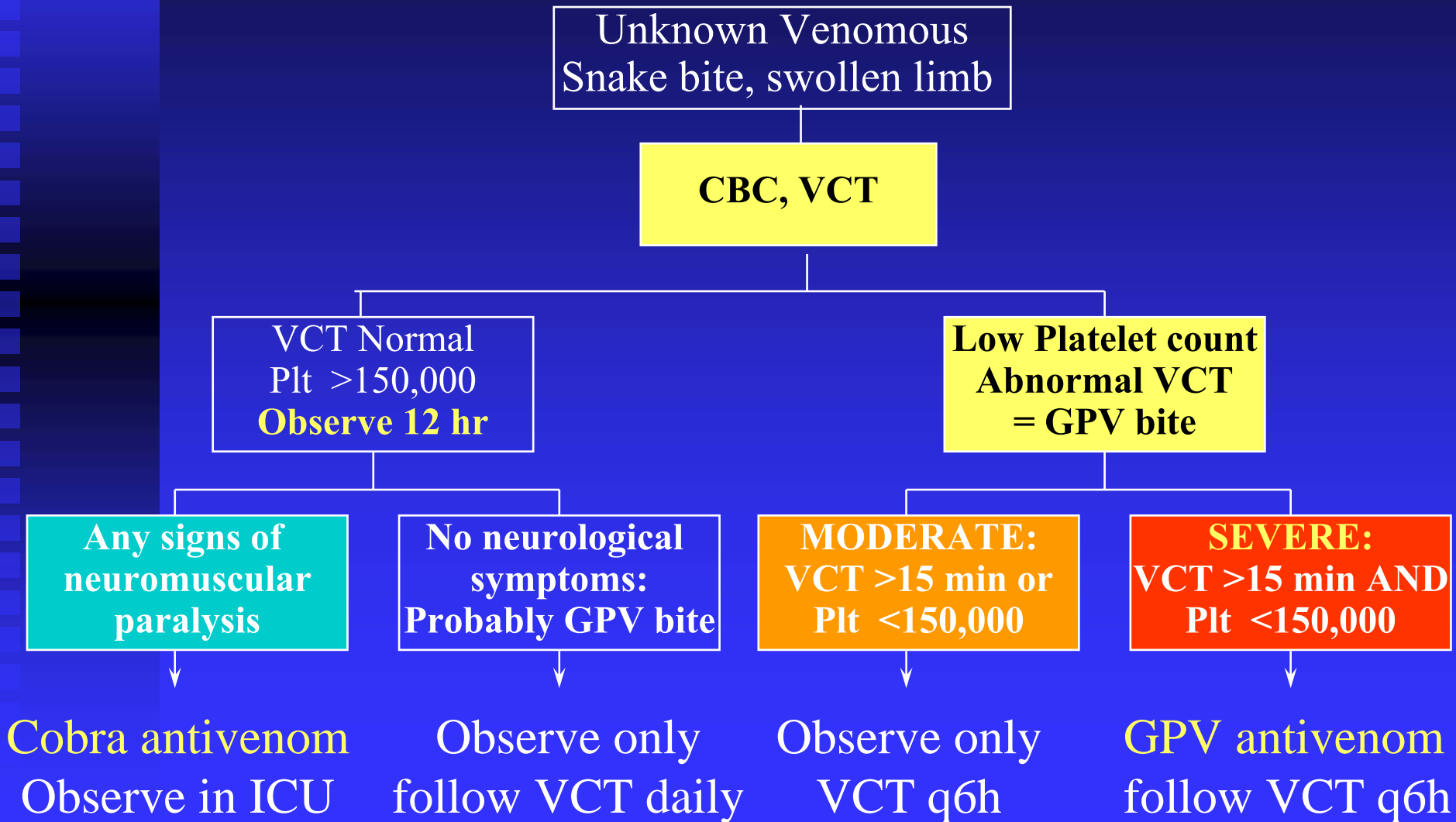
An approach to snake bite at C.U.



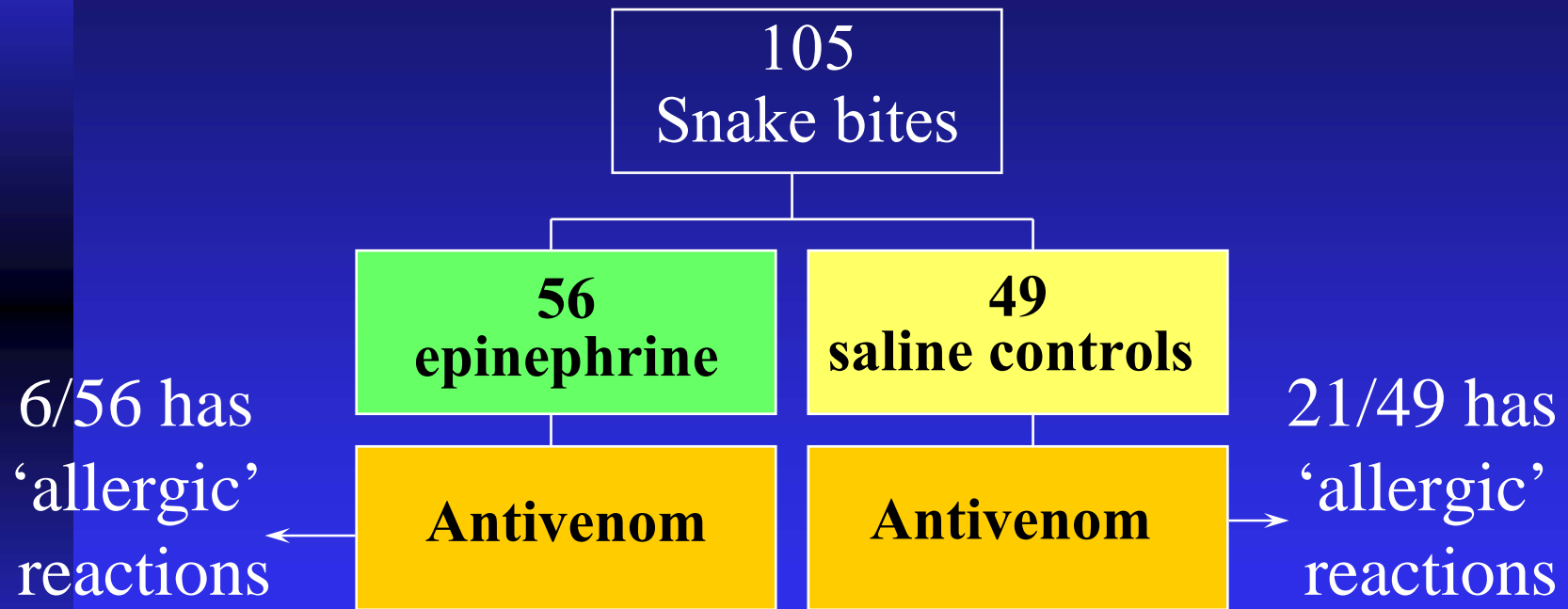
An approach to snake bite at C.U.



An approach to snake bite at C.U.

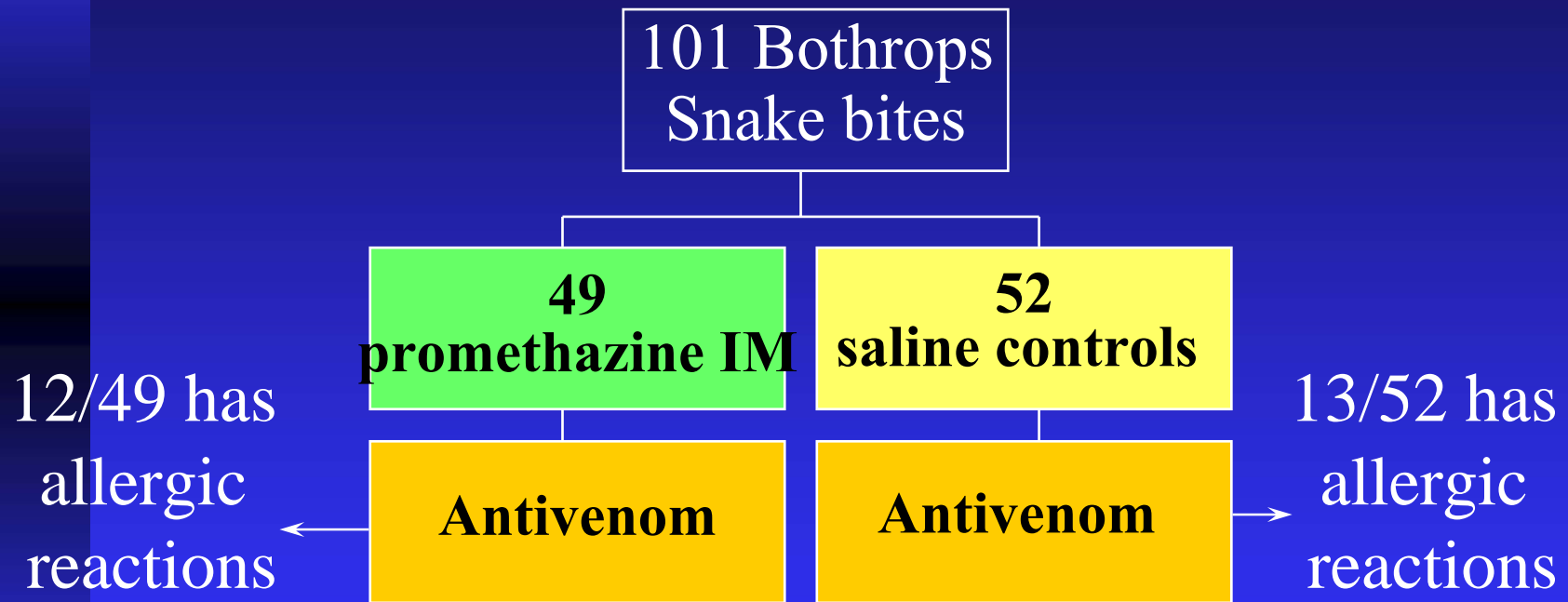


Preventing reactions to antivenom: Role of epinephrine



- Sri-lanka, any snake with prolonged VCT.
- Randomized double blind controlled trial: Polyvalent antivenom
- Adverse effect: tachycardia, no arrhythmia or hypertension

Preventing reactions to antivenom: Role of antihistamine



- Brazil; Bothrops snake bites
- Randomized double blind controlled trial: Polyvalent antivenom
- One pt in each group has severe anaphylaxis

Other venomous snake bites

■ King cobra (*Ophiophagus hannah*) งูจงอาง

- ◆ Case reports only: neurotoxic
- ◆ Usually **fatal** even though King cobra antivenom is available

■ Banded krait (*Bungurus fasciatus*) งูสามเหลี่ยม

- ◆ Rare, but curable: neurotoxic

■ Blue krait (Malayan krait,) งูทับสมิงคลา

- ◆ Fatal, Northeast Thailand,
- ◆ antivenom recently available

■ Sea snakes (several species)

- ◆ Rare but fatal, no antivenom available

Management of snake bite wounds

■ Reduction of limb edema

- ◆ Role of antivenom
- ◆ Role of steroid

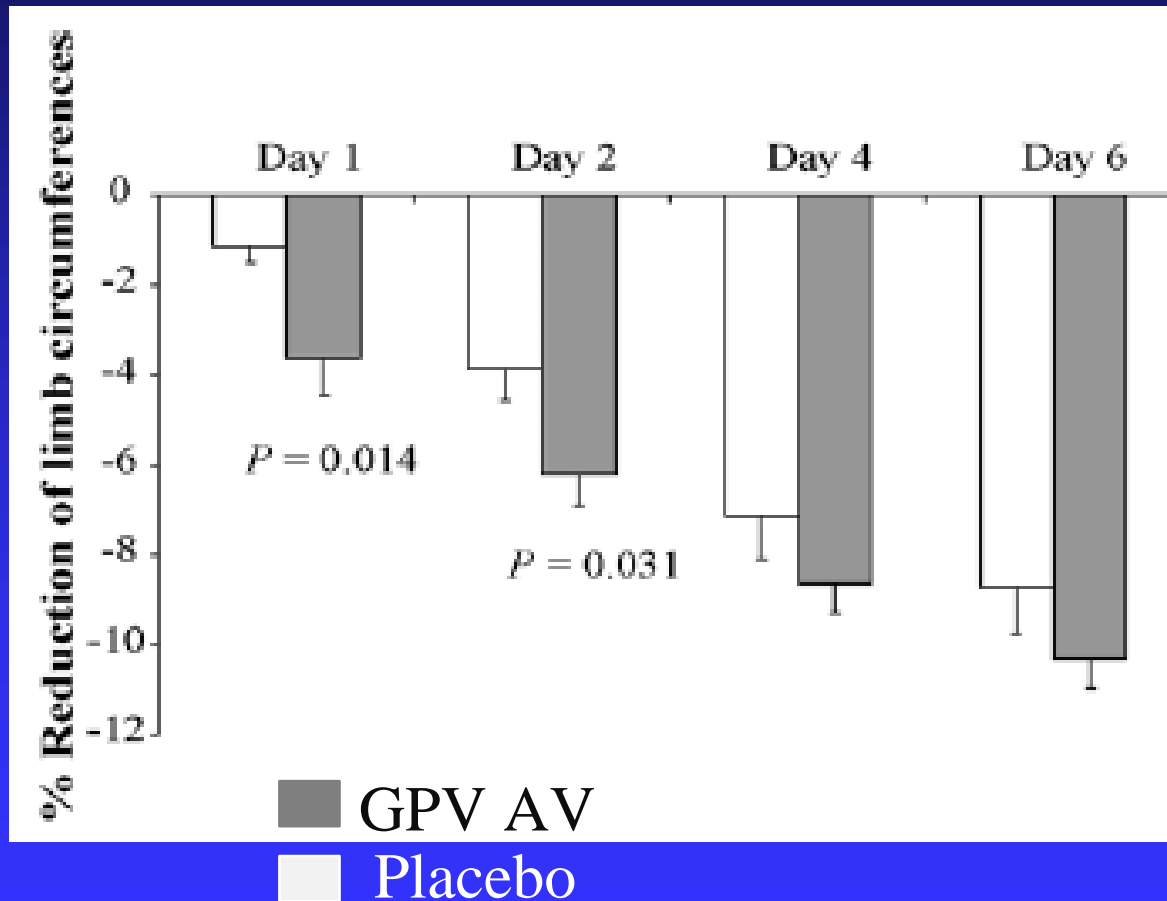
■ Wound infection

- ◆ Microbiology of snake bite wounds
- ◆ Role of prophylactic antibiotics

■ Role of tetanus prophylaxis

Reduction of limb edema: GPV bite

Antivenom can reduce limb edema



■ RCT

double blind

■ Severe edema
4.23 cm diff

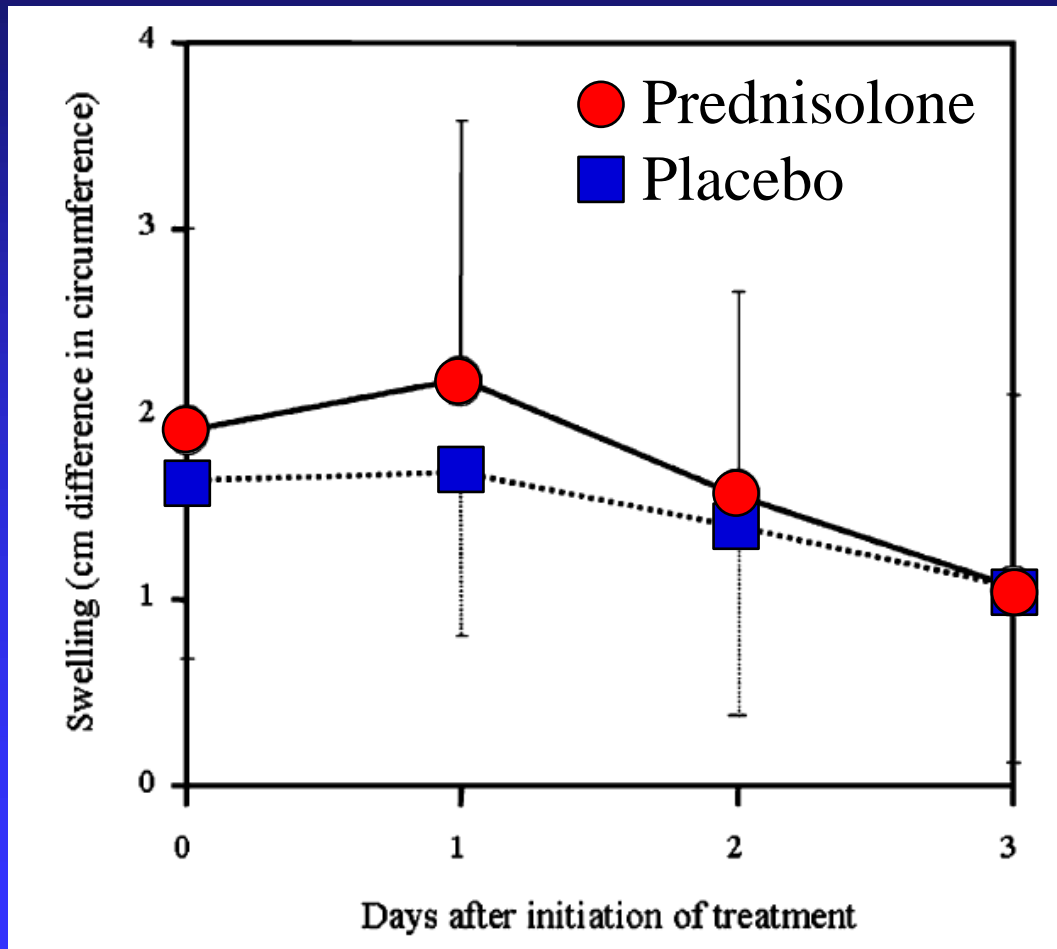
■ N=14 each

■ 2 vials IV vs
placebo

■ Rojnuckarin et al, Trans R Soc Trop Med Hyg 2005

Reduction of limb edema: GPV bite

Steroid is not useful for limb edema



- RCT
- double blind
- Any edema
- No AV
- N=22 v 21
- Prednisolone 1 mg/kg/d x3d vs placebo

Snake bite wounds: Microbiology

- Document **wound infection** is not frequent
- Skin necrosis can be extensive in
 - ◆ Cobra bite
 - ◆ Malayan pit viper bite
- **Wound culture** most often grows:
 - ◆ *Clostridium sp.*
 - ◆ Peptostreptococci
 - ◆ *Proteus spp.*
 - ◆ *Enterobacter sp.*
 - ◆ *E.coli*

Dhammabutara *et al* (1981) Siriraj Hosp Gaz 33:589-96.

Pongprasit *et al* (1985) Chula Med J 28:1109-16.

Snake bite wounds: Tetanus prophylaxis

- **Tetanus** is a cause of death in
 - ◆ Malayan pit viper bite (which is otherwise rarely fatal)
 - ◆ pre-tetanus toxoid era (1958-63)
 - ◆ (Warrell *et al* (1986) *Am J Trop Med Hyg* 35:1235-47.)
- **No clinical trial** on the use of Tetanus antitoxin or Tetanus toxoid: (unethical)
- Treat **snake bite** wound as **tetanus-prone wound**.

Snake bite wounds: Prophylactic Antibiotics



- Ecuador, Pit viper bites (Rattle snakes, moccasin, rattlers)
- A randomized controlled trial (unblinded)
- Gentamicin (1g/kg q8h) + Chloramphenicol (12 mg/kg q6h)
- Culture (+ve in 11/114) -> *E coli*, *Klebsiella*, *Enterobacter*, *Proteus* and *S. aureus*
- No statistical difference between 6/59 vs 3/55

Kerrigan *et al* (1997) *World J Surg* 21:369-73.

Snake bite wounds: Prophylactic Antibiotics



- **Bangkok**, Green Pit viper bites
- A randomized controlled trial (unblinded)
- **Amoxicillin** (40 mg/kg q8h) vs control
- **Clinical infection suspected in 3 patients each arm**

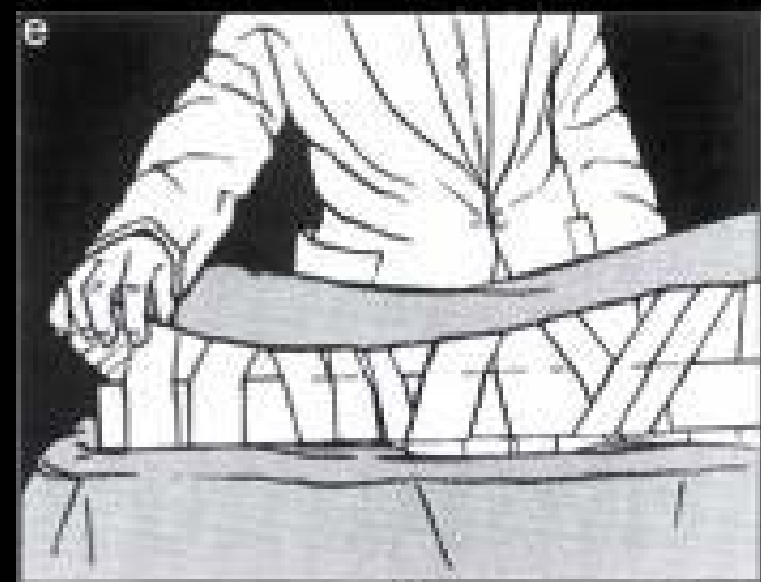
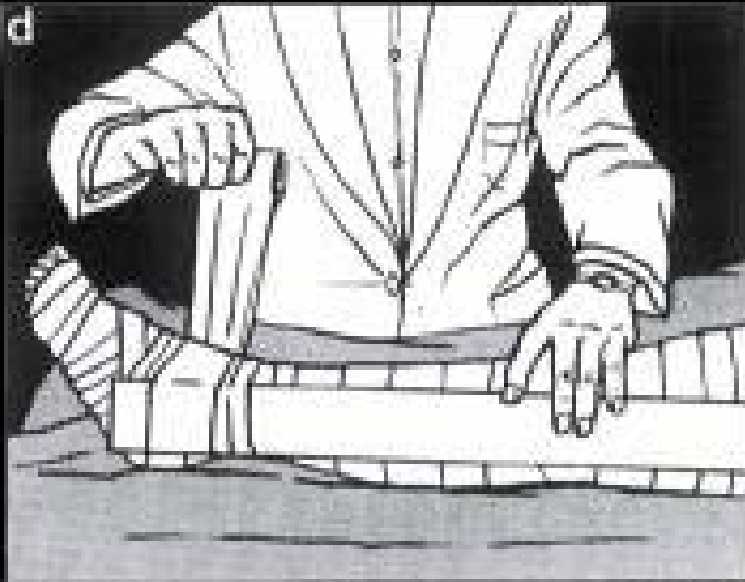
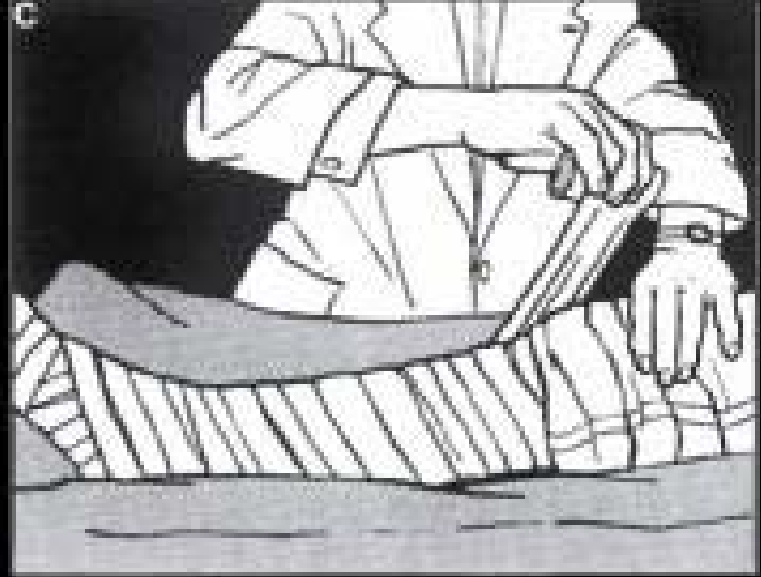
Snake bite wounds: Role of steroid

- Marked **edema** is seen in
 - ◆ Russell's viper
 - ◆ Malayan pit viper
 - ◆ Green pit viper : graded I - IV
- No published **clinical trial** on steroid use on snake bite wounds
- Our **trial** showed that low steroid do not reduce limb swelling faster than placebo

First Aid: Tourniquet?

- ◆ Beneficial for neurotoxin
(Watt G, et al. Am J Trop Med Hyg 1988)
- ◆ Does not prevent systemic absorption of hematotoxin
(Tun-Pe, et al. Trans R Soc Trop Med Hyg 1987)
- ◆ May cause ischemic necrosis

Pressure immobilization



Prevention: ชั้นปริตร

- **วิรูปักเขหิ** เม **เมตตัง**
- **เมตตัง** **เอราปะเถหิ** เม
- **ฉัพพยาปุตเตหิ** เม **เมตตัง**
- **เมตตัง** **กัณหาโคตะมะเกหิ** จะ
-

มา มัง **อปาทะโกหิงสิ**

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ข้าพเจ้าขอ**แม่เมตตัจจิตแก่**

- **งู**ในตระกูล **วิรูปักษ์**
- **งู**ในตระกูล **เอราบัด**
- **งู**ในตระกูล **ฉัพพยาบุตร**
- **งู**ในตระกูล **กัณหาโคดม**
-**สัตว์ไม่มีเท้า** สัตว์
สองเท้า สัตว์สี่เท้า สัตว์เท้า
มาก

สัตว์ไม่มีเท้าอย่าได้เบียดเบียน
ข้าพเจ้า

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 - ◆ Paul Garner (Infectious disease group)
- Snake pictures from:
 - ✚ ไพบูลย์ จินตกุล และ ลาวัญญ์ จันทรโสม ภูพิชในเมืองไทย โรงพิมพ์
จุฬาลงกรณ์ กทม. 2540