# NEWS FROM THE PIT

Arizona Poison and Drug Information Center

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1-800-222-1222

## Platelets and Fibrinogen

**Have we figured out blood yet?**

**By Thom Maciulewicz, PharmD BCPS**

In 1910, Dr. William W. Duke defined the role of platelets in hemostasis through a bleeding time test and demonstrated the benefit of blood transfusion for thrombocytopenia. The bleeding time test involved placing a standardized cut on the ear lobe, blotting the cut every 30 seconds, and waiting until the bleeding stopped (normal cessation was ~3 minutes). At the bedside, three thrombocytopenic patients with severe bleeding were given a whole blood transfusion and Duke watched the bleeding times improve from 60 minutes to 3 minutes. His “spidey sense” began to tingle and he realized that by fixing the anemia, he decreased the severity of the bleed. When platelets began to fall again, hemorrhage worsened.

Still intrigued, the good doctor headed into the lab to further test his newfound discovery. In the lab, dogs were rendered thrombocytopenic by administration of benzol (aka benzine), which is known to suppress platelet production. He observed that hemostasis was able to be maintained despite decreasing platelet counts, but when they fell below 30,000/mcL, the likelihood of spontaneous hemorrhage increased.

### NEWSLETTER HIGHLIGHTS

**Numerous hemotoxins in snake venom have varying mechanisms of how they affect hemostatis**

# Platelets and Fibrinogen

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Big takeaways from this were: 1) There is something else going on in the blood regarding hemostasis. Actually, a whole lot… like that clotting cascade you learned about in school with the bazillion factors, enzymes, and platelets, 2) We now had a test to examine the blood and determine the risk for bleed. The use of bleeding time catalyzed the field of medicine to discover other hematologic disorders, risk factors for bleeding, and advancements in blood hemostasis monitoring, and 3) The concept of a trigger to infuse platelets based on specific levels was born (popularized in chemotherapeutics during 1950's). Like I said, this was a big deal.

All of our previous newsletters on rattlesnake envenomation (RSE) have been talking about one thing and one thing only: the blood. It's been over 100 years since Duke was obsessing about blood and here we are today: still obsessed about it (especially, in regards to envenomation). What is wrong with us, why are we still doing this, and have we figured out blood yet? Well, sort of, but there is quite a bit to unwrap. If you have ever managed a snake envenomation before or had a Poison Control Center help you with caring for these patients, you know there is a rainbow of lab tests to perform. Specifically, we want to take a look at the complete blood count (platelets, hemoglobin, hematocrit), prothrombin time (PT), INR, and fibrinogen. As there are numerous hemotoxins in snake venom, they have varying mechanisms of how they affect hemostasis and thus, we examine the blood from different angles.

Dr. Tyler Hoelscher was kind enough to refresh our memories in the previous newsletters on the clotting cascade, the activation of platelets allowing them to aggregate, and fibrinogen aiding the formation of a fibrin/platelet clot. We also learned that rattlesnake envenomation produces a DIC-like picture called venom-induced consumptive coagulopathy (VICC), which produces laboratory abnormalities such as thrombocytopenia, a prolonged PT, an elevated INR, or hypofibrinogenemia.

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So, now you are probably saying to yourself, can we just give antivenom to counteract and halt the hemotoxic effects and finally stop talking about blood? Not just yet, but thanks for bringing up antivenom! While we are at it, let's talk about platelets and fibrinogen. In the initial stages of a RSE, I want to know the baseline fibrinogen and platelets (amongst other things like past medical history, physical assessment of bitten limb, vital signs, etc.). I want to know where I'm starting at baseline because RSE is a dynamic course and not every patient will have the same progression/resolution. One of our attendings has this saying, "If you've seen one rattlesnake bite, you've seen one rattlesnake bite".

A few categorical responses of platelets and antivenom have been observed from our poison center in thousands of cases over the last 20 years. First, the patient has thrombocytopenia prior to any antivenom. We give antivenom and the platelets magically rebound, but do not quite make a full recovery. Remember, snake venom has many toxins! In this case, platelet aggregation from the venom was able to reversed by antivenom. Additionally, in RSE there is usually some degree of swelling/inflammation and vascular damage local to the bite site. Platelets are recruited to the area as part of the inflammatory healing process and recovery of platelet count will be slow due to regeneration.

In the second scenario, we give antivenom to the thrombocytopenic patient and the platelets do not rebound as in the previous case. This could be due to either destruction of platelets or maybe more antivenom is needed to counter a heavier venom load. If the patient has any signs or symptoms of systemic toxicity (nausea, vomiting, hypotension, bradycardia) or uncontrolled progression of swelling/tissue damage along with the thrombocytopenia, more antivenom is likely needed. Okay, still with me? This last section gets a little dicey.

Lastly, we encounter patients with a biphasic thrombocytopenia. Initially, the platelets will rebound following antivenom, then hours later have a fall in platelets. In the second wave of thrombocytopenia we have observed platelet levels that rebound after antivenom and those that do not. When they do respond, it's likely due to a venom depot with delayed release from being trapped somewhere due the initial swelling and inflammation. In the case where antivenom appears to not improve platelet levels, this could be due to destruction, or because venom caused the platelets to be taken up (via macrophages) and cleared by the liver.

*If you've seen one rattlesnake bite, you've seen one rattlesnake bite.*

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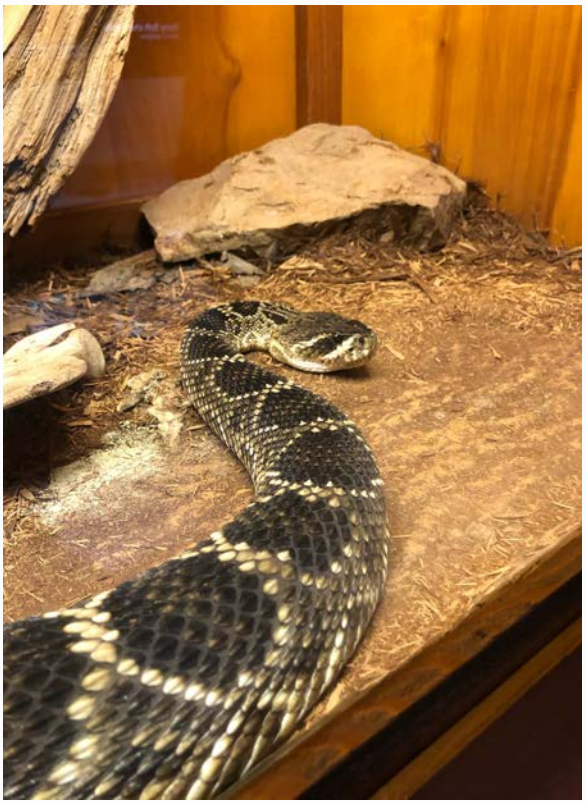
Phew, that was intense! As you can see there is a lot to consider regarding the diverse mechanisms venom can have on platelets alone. In this manner, we can monitor platelets to see how venom is initially behaving, the response to antivenom, and if more antivenom administration is warranted in conjunction with physical assessment of the patient.

Lastly, we will talk about fibrinogen, from the Latin fibra “fiber, filament”. In 1666, Marcello Malpighi noticed while examining cardiac thrombi that red blood cells were clumped together with a meshwork consisting of fibers. It wouldn’t be until the mid to late 1800s that fibrinogen would be officially named and scientists were able to demonstrate the process of fibrinogen transforming into fibrin. So, we just literally just missed fibrinogen’s 350th discovery birthday in 2016!

Hypofibrinogenemia following RSE is due to thrombin-like enzymes cleaving fibrinogen. Fibrinogen can no longer polymerize, forming a mesh web to catch and adhere more platelets together. Instead, we get small weak strands, which are easily degraded. Unfortunately, this means giving antivenom will not cause a rapid rebound as observed with platelet aggregation. However, antivenom should protect fibrinogen from any further slicing and dicing by circulating venom. Fibrinogen is also an acute phase reactant, meaning during the course of inflammation, infection, and injury the body responds by ramping up fibrinogen production. Finally, some good news! Meaning, we can fend off the effect of venom on fibrinogen and allow for the body to regenerate adequate levels of fibrinogen in a relatively short amount of time (hours to a day).

**We can fend off the effect of venom on fibrinogen and allow for the body to regenerate adequate levels of fibrinogen.**



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Remember, when assessing a RSE we're not just sending labs out willy-nilly. We want to know where the patient's laboratory hemostasis is at baseline, monitor them following antivenom administration, and then for a sufficient amount of time afterwards. In essence, we are not necessarily looking at a lab number to determine bleed risk, but also to investigate if venom has been adequately neutralized and no longer a threat. In the last 20 years our poison center has helped to care for thousands of RSE and only a very small percentage of them had any significant bleeding. Moreover, we have had zero deaths due to bleeding in that time period thanks to prompt treatment with antivenom. If you ever need help caring for an envenomated patient and assistance deciphering lab trends, please do not hesitate to contact your local poison center at 1-800-222-1222. A toxicologist is just a phone call away!