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Diagnosis of human envenoming by terrestrial venomous animals: Routine, advances, and perspectives

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ABSTRACT

Despite the development of new and advanced diagnostic approaches, monitoring the clinical evolution of accidents caused by venomous animals is still a challenge for science. In this review, we present the state of the art of laboratory tests that are routinely used for the diagnosis and monitoring of envenomings by venomous animals, as well as the use of new tools for more accurate and specific diagnoses. While a comprehensive range of tools is outlined, comprising hematological, biochemical, immunoassays, and diagnostic imaging tools, it is important to acknowledge their limitations in predicting the onset of clinical complications, since they provide an overview of organic damage after its development. Thus, the need for discovery, validation, and use of biomarkers that have greater predictive power, sensitivity and specificity is evident. This will help in the diagnosis, monitoring, and treatment of patients envenomated by venomous animals, consequently reducing the global burden of morbidity and mortality.

1. Introduction

Envenomings by venomous animals has increasingly affected the population of tropical and subtropical countries, resulting in high rates of morbidity and mortality. Snakebite envenomings have represented the main neglected health problem regarding venomous animals in tropical and subtropical countries in Africa, Asia, America, and Oceania (Braitberg et al., 2021; Cavalcante et al., 2021, 2023a,b; Chippaux, 2017; Chippaux et al., 2019; Hannan Wan Ibadullah et al., 2021; Mender et al., 2022). Approximately 2.7 million people may be affected annually, resulting in 81,000–138,000 fatal cases and 400,000 cases of morbidity (Longbottom et al., 2018). The problem has increased over the years and after its inclusion in category A of neglected diseases by the World Health Organization (WHO) in 2017, strategies to mitigate the problem have been proposed, and in 2020 the race against cases of morbidity and mortality caused by snakebite was initiated through The Global Snakebite Initiative (Minghui et al., 2019).

Arthropod bite envenoming has also gained substantial attention due to the increase in cases. Scorpions kill less than snakes, although have been responsible for higher number of accidents, representing a serious public health problem in the Old and the New World, especially for pediatrics (Chippaux and Goyffon, 2008). Spider accidents report an exceptionally low number of fatalities, leading to an underestimation of their clinical significance. The reasons behind our exaggerated perception of the risk associated with spiders remain unclear (Cain et al., 2023; Fusto et al., 2020; Hubbard and James, 2011; Isbister and White, 2004; Mammola et al., 2022). Finally, the growing number of cases of envenoming by Africanized bees has represented a new challenge in clinical Toxinology. The mechanisms involved with the development of clinical complications have not yet been explored, and even today, there are no

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specific diagnoses and an antivenom available for treatment, although these are under development (Barbosa et al., 2017, 2021).

Therefore, a significant aspect of the issue pertains to the necessity for a deeper comprehension of the mechanisms driving these pathophysiological effects (Albuquerque et al., 2020; Cavalcante et al., 2021, 2023a,b; Pereira et al., 2023; Pucca et al., 2019b). This need is compounded by the absence of a clear and specific diagnosis, alongside a dearth of predictive tools for the emergence of various clinical complications. Consequently, these factors contribute to elevated rates of tissue loss, amputations, and fatalities (Cavalcante et al., 2023a,b). Within this context, this review delves into current and emerging methodologies for diagnosing and monitoring envenoming caused by major terrestrial venomous animals responsible by human envenoming. In the future, certain diagnostic tools discussed here might find their way into clinical use. This review also aims to facilitate the development of clinical trials that validate these tools by highlighting the most promising methods.

2. Snakebite envenoming

Snakebite envenoming is a tropical disease distributed in the developing world (Longbottom et al., 2018), such as in some Asian and African countries (Chippaux et al., 2019; Wang et al., 2023), Latin American (Chippaux, 2017), and Oceanian (O'Leary and Isbister, 2009) countries. The greatest burden of snakebite has been identified in South Asia and sub-Saharan Africa (Appiah, 2012). India has the highest incidence of snakebite mortality ranging from 13,000 to 50,000 cases per year (Alirol et al., 2010; Mohapatra et al., 2011; Warrell, 2010). In the Americas an average annual incidence of 57,500 snakebites (6.2 per 100,000 population) and mortality close to 370 cases of death (0.04 per 100,000 population) is reported, although rates vary widely between and within countries (Chippaux, 2017).

Many viperids' venoms are capable of inducing pain, edema, inflammation (Cavalcante et al., 2023a,b) oxidative stress (Dong et al., 2020) and activation of immunocompetent cells (Teixeira et al., 2019), immunomodulatory activity (Pedro et al., 2024), hemostatic alterations and bleedings (Larréché et al., 2021), acute renal damage (Albuquerque et al., 2020), rhabdomyolisis and necrosis (Fujioka, 2015; Gutiérrez et al., 2018). On the other hand, envenoming by elapid serpents is mainly distinguished by inducing a neurotoxic syndrome. PLA_2s and 3FTX act as antagonists of ion channels and nicotinic or muscarinic receptors of pre- or post-sinaptic junctions, causing neurotoxicity (Ranawaka et al., 2013). The pathologic phenotype is characterized by flaccid paralysis, which is at first evident as bilateral ptosis and ophthalmoplegia. Moreover, the flaccid neuromuscular paralysis is descending, which can worsen by affecting the bulbar block (mouth and throat muscles responsible for speech and deglutition) and respiratory muscles (Gutiérrez et al., 2017).

In snakebite, uncertainties persist regarding the species involved (de Castañeda et al., 2019), the quantity of venom injected, and the appropriate dosage of antivenom administered (Daswani, 2017; Pucca et al., 2020b). In addition, venom composition may vary, influencing the snakebite manifestations (Moretto Del-Rei et al., 2019), make it difficult for health professionals to make decisions. Frequently, the healthcare teams overseeing the clinical care of victims at district and rural hospitals lack the essential expertise and tools required to determine the most effective course of action for optimizing therapeutic outcomes within a timely manner (Cristino et al., 2021). However, although several techniques have been performed routinely, while others have been explored for application, diagnosis remains a challenge (Fig. 1).

In this context, the proper identification of the snake genus and/or type of venom can allow physicians to predict the development of clinical manifestations, which may modify the clinical outcome (Cavalcante et al., 2023a,b). To improve the clinical team's understanding of this task, there is a common and deceptively simple categorization of venoms as being primarily neurotoxic (*Elapidae* family) and proteolytic and/or hemotoxic (*Viperidae* family) (Liu et al., 2018),

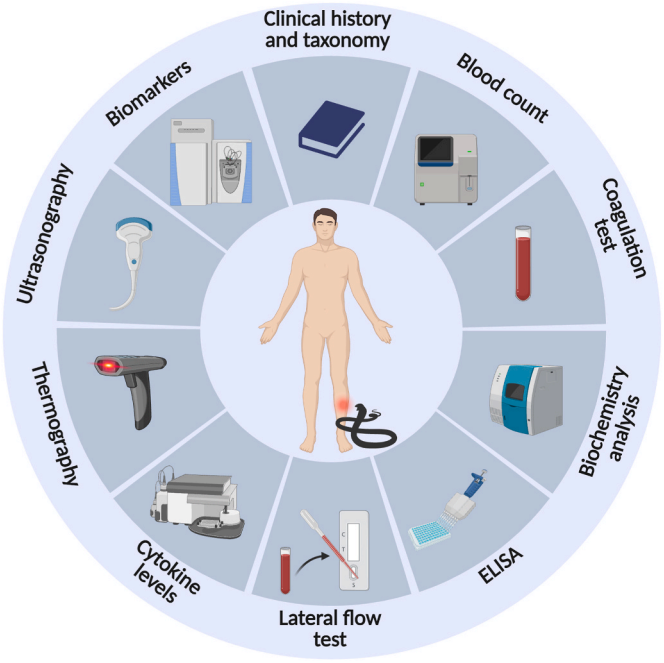

Fig. 1. Overview of methods routinely used and under development for the diagnosis and monitoring of patients victims of snakebite envenoming.

which can lead to clinical misinterpretations, with several important exceptions to the standard clinical pictures.

In recent years there has been renewed interest in innovations and improvements, with much research being published not only on new treatment modalities (Pucca et al., 2019a). However, new diagnostics tools, such as immune-diffusion, agglutination test, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, lateral flow assay (LFSA), polymerase chain reaction, infrared thermography, and others, have not been implemented in the snakebite clinics (Knudsen et al., 2021). Thus, even amidst diagnostic advancements, the identification of snakebite envenoming continues to be based on a combination of patient history, clinical presentation, and routine laboratory analysis (J. dos S. Cavalcante et al., 2023a,b).

In Latin America, many countries consider coagulation time as a commonly investigated parameter for early detecting viper snakebite envenoming, due to the highest occurrence of envenoming by snakes causing coagulopathy. Thus, a series of tests are used to identify and monitor coagulation abnormalities, including the 20-min whole blood coagulation test (20WBCT), Modified Lee and White (MLW) method, bleeding time, prothrombin time, and activated partial thromboplastin time (APTT) (Hamza et al., 2021; Lamb et al., 2021; Suseel et al., 2023). Hematological analysis based on cell counts has also been used. Clinically, cases of microangiopathie thrombotique have been reported and associated with kidney injury and thrombocytopenia after envenoming by *Bothrops jararaca* and *B. erythromelas* in Brazil (Bucaretchi et al., 2019; Mota et al., 2020; Noutsos et al., 2019, 2022). However, markers of microvascular hemolysis and anemia after snakebite are not yet specific (Noutsos et al., 2022). Platelet count, used to detect thrombocytopenia, lacks specificity concerning the genus and type of venom, due to the variability of the action of toxins on platelets, which can cause platelet aggregation or inhibition (Almeida et al., 2023). Intense neutrophilia and thrombocytopenia have been documented in snake envenoming cases involving tissue loss and/or limb amputations but late when tissue damage has already occurred (Luciano et al., 2009; Magalhães et al., 2017; Valente-Aguiar et al., 2019) a low predictive potential for the clinical outcome.

Additional challenges stem from the reliability of test results concerning the patients' clinical status. For instance, in the Amazon region,

46% of *B. atrox* snakebite cases exhibit no alterations in whole blood coagulation tests, while 90% do not present thrombocytopenia upon arriving at the clinic (Oliveira et al., 2020; Silva de Oliveira et al., 2020). On the other hand, in *B. jararaca* snakebites, 100% of cases present thrombocytopenia and leukocytosis by the time they arrive at the clinic (Santoro et al., 2008). This underscores the necessity to customize protocols for diagnosing, managing, and treating envenoming in Brazil, whilst hematological parameters serve as crucial markers for patient monitoring and play a pivotal role in determining the number of antivenom vials required for treatment.

Biochemical parameters are used to monitor acute envenoming; however, their specificity and sensitivity are limited, and may not reflect the patient's true clinical condition. For instance, assessing creatine kinase (CK), an enzyme involved in ATP degradation with a relatively short half-life, reveals activity that swiftly normalizes after myodegeneration or local necrosis ceases (Smith et al., 2013). Although it has been considered a gold standard for assessing muscle damage, evidence has shown that this biomarker does not reflect the amount of tissue damage (Delanghe et al., 2019; Lippi et al., 2018), since its activity depends not only on the number of CK molecules present in plasma/serum, but also to the glutathione concentrations that tend to decrease during rhabdomyolysis (Delanghe et al., 2019).

ELISA and LFSA for detection of venom in patient blood samples have also been developed (Kulawickrama et al., 2010; Liu et al., 2018). However, ELISA and LFSA have some limitations. For example, certain protein classes within each venom overlap, causing detection devices using immunological techniques to be nonspecific, identifying a range of species rather than a specific one (Knudsen et al., 2023). Another critical factor to be considered is the amount of injected and free venom in the patient's plasma in relation to the sensitivity of the kit, since toxins might be significantly diluted in plasma samples, potentially falling outside the kits detection range. (Liu et al., 2018).

However, recently, some LFSAs kits are considered as a promising tool for detection of *Trimeresurus stejnegeri*, *Protobothrops mucrosquamatus*, *Bungarus multicinctus,* and *Naja atra* venoms in human blood (Liu et al., 2018; Nong et al., 2023). Associated to this the high rates of sensitivity and specificity without cross reactivity identified by a LFSA kit, specifically, to the venom of *Naja atra* indicates that an immunochromatographic strip assay might be suitable for snake venom detection and used as a quick diagnostic tool against the burden of snakebite in the future, since the LFSAs kit technique is largely known and applied in emergency's situations across the world (Koczula and Gallotta, 2016; Qriouet et al., 2021).

Research into clinical manifestations of envenoming indicates that cytokine responses could serve as potential biomarkers for snakebite envenoming. For instance, patients bitten by *Bothrops* spp. and *Crotalus durissus terrificus* demonstrated elevated serum levels of cytokines like IL-6 and IL-8, while levels of IL-1β and TNF-α in blood samples remained unchanged (Barraviera et al., 1995). In contrast, *B. atrox* patients demonstrated an increase in the levels of CXCL-9, CXCL-10, IL-6, IL-2, IL-10, and IL-17A molecules. In general, in *Bothrops* envenoming, CXCL-8 and CCL-2 cytokines shows elevated on admission and progressively decreased during the clinical evolution of patients bitten after antivenom administration (Neves et al., 2022), while in some cases CXCL-8 and IL-2 showed significantly lower levels in patients who clinical conditions progressed to Early Adverse Reactions (EARs) to antivenom treatment (Soares et al., 2022).

Diagnostic imaging tools have also been studied in the diagnosis and monitoring of snake envenomings (Medeiros et al., 2019). Thermography is a technique that quantifies the body surface temperature, capturing the thermal radiation emitted and producing a high-resolution digital image called a thermogram. Its use makes it possible to visualize the extent of the inflammatory process and tissue damage caused by snake venom in Brazil through the analysis of the thermal gradient between the bitten limb and the healthy one (Medeiros et al., 2019; Ribeiro et al., 1969).

In snakebite envenoming, fever in patients may not represent an infectious condition but an inflammatory or immunomodulated process, being an important differential etiology in such cases (Ribeiro et al., 1969). The presence of hot spots and local alterations in tissue's temperature of bitten patients have been accessed by infrared thermal technique and interesting results were found for differentiating venomous snakebites from non-venomous and dry bites (Sabitha et al., 2021). Based on this, the area of increased temperature in the hot spots is evident on infrared thermal imaging in envenomed patients, while hot spot was not evident in most patients without envenoming, showing that infrared thermal images had a high sensitivity and specificity to differentiate envenomed patients from those without (Sabitha et al., 2021).

Ultrasonography has also been studied as a resource to measure the extent of edema and the rate of proximal progression (Ho et al., 2021; Ismail, 2015; Jolissaint et al., 2018; Vohra et al., 2014; Wood et al., 2016). Ultrasonography has been shown to be a tool with multiple clinical applications in snakebite envenoming, including the identification of damaged tissue in the intramuscular layer (Wood et al., 2016) and compromised arterial flow (Mc Loughlin and Mc Loughlin, 2013; Mc Loughlin et al., 2013). In muscle damage, the ultrasonography demonstrated the structural involvement of superficial tissues that were damaged (presence of subcutaneous edema, fasciculations and tendon sheath fluid — a marker of tenosynovitis), and the preservation of deeper tissues in cases of crotaline snakebite (Vohra et al., 2014). Ultrasonography has also been used for renal analysis, revealing the presence of spontaneous subcapsular and perinephric hematoma, increased size of the kidneys and kidney damage at different stages (Golay et al., 2015; Patil, 2012; Pucca et al., 2020a; Tchaou et al., 2020). These findings suggest that ultrasound can aid in the external assessment of bite-related injuries by providing useful information on internal changes.

Point-of-care ultrasound protocol could improve the capacity for facilitating the clinical decisions for antivenom administration, once the anatomic site of the snakebite is an important factor that affects the prognosis of the patients (Ho et al., 2021). Furthermore, ultrasound-guided compression alone or in combination with some substances as thrombin, can reduce some neurotoxic effects of *Daboia russelii* that induced pseudoaneurysm, without surgical procedure. However, several limitations in this technique can be pointed, such as envenomated limb or a comparison with the generally accepted invasive evaluation for acute compartment syndrome (Ho et al., 2021).

Clinical proteomic studies consider the set of proteins in an organism on a large scale, making it possible to identify biomarkers associated with severity, progression, and therapeutic response to treatment. The wide range of protein recognition and associated biochemical processes provides a solid basis for application in the diagnosis of human diseases, such as snake envenoming. However, this application started recently. First, in vivo studies revealed the possibility of identifying candidate proteins for biomarkers associated with the severity of edema and according to the amount of venom injected into mice (Cavalcante et al., 2022a, 2022b, 2022c). Regarding this, peroxiredoxin 2, hemoglobin subunit alpha, and Factor IX, increased according to the amount of *B. atrox* venom injected, while Igf1, Efemp1, and fibulin showed a drop in the plasma levels of Igf1, Efemp1, and fibulin (Cavalcante et al., 2022b). On the other hand, *B. erythromelas* venom induced an increase in plasma levels of apolipoprotein A1, serum amyloid protein A-4, adiponectin, in addition to a drop in plasma levels of fibulin 1, Factor XII and vitamin K-dependent protein Z (Cavalcante et al., 2022a). Clinical proteomics studies also enabled discrimination between envenomings caused by *Agkistrodon acutus* and *Trimeresurus stejnegeri* (Dong et al., 2020). Finally, another study based on clinical proteomics detected potential markers indicative of lethal anaphylaxis, cardiac arrest, and brain death in an individual case of lethal of snakebite envenoming by *Crotalus viridis viridis*, which is in accordance with the clinical course of the envenoming, since the patient developed a rapid, apparent and lethal anaphylactic reaction, characterized by collapse, cardiac arrest, and eventual

brain death (Smith et al., 2023).

3. Scorpion envenoming

Although the taxonomic catalog is extensive, about 30 species of scorpions are considered harmful to humans, 29 of which belong to the *Buthidae* family. While scorpions kill less than snakes, the effects of scorpion envenoming represent a serious public health problem, particularly for pediatrics, and affect mainly countries in the Old World (Iran, Saudi Arabia and Morocco, Africa, Asia, and Europe) and the New World (Mexico, Brazil, and Venezuela, United States, Central America, Caribbean, and other South American countries) (de Oliveira et al., 2024; Mendoza-Tobar et al., 2024; Ward et al., 2018).

There are still no laboratory tests or diagnostic tools for scorpion envenoming (Abroug et al., 2020). However, scorpion stings are typically intensely painful, facilitating patients' descriptions of the incident, especially since victims frequently witness the animal and often bring it along for identification (Monteiro et al., 2016). In addition, in instances where the victim did not witness the animal, the diagnosis can be guided by a combination of factors related to the incident (location, pain, clinical signs, among others) (Chabchoub et al., 2010). Although scorpion envenoming has a major impact on public health, and venom identification and quantification tools are necessary, this is a subject that has been little explored. Thus, the use of antivenoms for treatment is based on the clinical picture presented by the victims (Abroug et al., 2020; Monteiro et al., 2016; Thumtecho et al., 2023a). This issue can lead to errors regarding the administration or not of antivenoms, and, in cases where the application is necessary, errors regarding the amount of antivenom to be administered (Santos et al., 2016).

The classification of scorpion sting envenoming continues to this day based on the set of clinical manifestations, being: (i) dry sting (without envenoming), (ii) class I (only local manifestations); (iii) class II (non-life-threatening clinical manifestations), (iv) class III (life-threatening systemic manifestations - respiratory failure, pulmonary edema, cardiogenic shock, and brain damage) and fatal outcome (Khattabi et al., 2011). Biochemical parameters are used to monitor acute envenoming: Leukocytosis, hypokalemia, hyperglycemia, and glycosuria. Increased CK levels due to CK-MB and CK-BB fractions, increased levels of lactate dehydrogenase, AST, and amylase (Cupo et al., 1994). Furthermore, many patients initially considered moderate do not receive antivenom, and this is due to the long period of observation, in which monitoring occurs only by the clinic, although some laboratory tests can auxiliary (Takehara et al., 2023). ELISA assays represent promising tools for detecting *Tityus serrulatus* venom in the plasma of patients in moderate and severe cases, yet they lack the ability to distinguish between cases of envenoming and healthy individuals (Rezende et al., 1995). Other studies also report the ability to detect and quantify scorpion venom antigens in the serum of patients (Benslimane et al., 2000; D'Suze et al., 2003; Krifi et al., 1998; Osnaya- Romero et al., 2016). In this sense, advances in the field of scorpion venom real-time detection using electrochemical or circular dichroism approaches have been realized (Hartono et al., 2009; Mars et al., 2018; Mazhdi and Hamidi, 2021). A liquid crystal-based sensor for real-time and label-free identification of phospholipase-like toxins like phospholipases, beta-bungarotoxin (*B. multicinctus*), alpha bungarotoxin (*B. multicinctus*) have already been reported. Hydrolysis of the self-assembled phospholipid monolayer at the aqueous-LC interface by betabungarotoxin induces orientation responses of LCs, emitting optical signals that can be used as diagnostic tools (Hartono et al., 2009). Another amperometric biosensor to detect scorpion venom toxins displaying rapid body diffusion has also been reported, with the ability to identify low levels of *Androctonus australis hector* (Aah) venom. The sensitive and robust sensing platform is built by combining the unique features of graphene quantum dots and the high selectivity of the best-in-class nanobody candidate (NbF12-10) generated to fight scorpion envenomation. To amplify the signal, a Hydroquinone/H2O2/peroxidase system was used, obtaining high sensitivity (Mars et al., 2018). Finally, *Odontobuthus doriae* scorpion venom and its neurotoxic effect on blood serum neurotransmitter analytes were detected with high sensitivity using the achiral plasmonic structure as a sensor (Mazhdi and Hamidi, 2021).

When the manifestations are systemic, the electrocardiogram is very useful, since the patients may present cardiac alterations (Abdi et al., 2013). In addition, radiography and echocardiography are used to investigate possible changes in the cardiac area, as well as signs of acute pulmonary edema and other cardiac complications (Bahloul et al., 2013; Kumar and Naveen Prasad, 2015; Thumtecho et al., 2023b). Furthermore, cases of cerebral edema and neurological deterioration have been reported, being diagnosed first by clinical manifestations, and confirmed by computed tomography (Romero and Hernández, 2005).

4. Honeybee stings

Honeybee envenoming can lead to a complex physiopathological response, including inflammatory reactions, allergic manifestations, anaphylactic shock, and systemic toxic reactions (Cavalcante et al., 2024). Over the last few years, the number of accidents involving Africanized bees has increased (*Apis mellifera*) (Pucca et al., 2019c). Local reactions observed in these envenomings include papules, pain, erythema, local burning and edema. In some previously sensitized patients, severe systemic allergic reactions, culminating in anaphylactic shock, may occur (Ediger et al., 2018). However, a wide range of clinical complications resulting from multiple bee stings have been documented, and include, in accidents with multiple stings (>100), systemic reactions such as liver injury, renal failure, myocardial infarction, hypotension, acute lung injury and acute respiratory distress syndrome can occur and progress to multiple organ failure and death (Akyıldız et al., 2016; Babikir et al., 2021a; Guzel et al., 2016; Lubis et al., 2019; Navaradnam et al., 2021).

Hemorrhage can manifest in multiple locations after a bee sting, potentially affecting different body systems. These areas include the digestive system (resulting in gastrointestinal hemorrhage), the nervous system (leading to subarachnoid hemorrhage and hemorrhagic stroke and others) (Abhishek et al., 2021; Akyıldız et al., 2016; Babikir et al., 2021b; Gupta, 2019; Jain et al., 2012; Kabra et al., 2022; Ramlackhansingh and Seecheran, 2020; Rathnayaka et al., 2021; Varuni et al., 2018), and the respiratory system (causing pulmonary hemorrhage) (Mondello et al., 2023), and others. Furthermore, hematological complications that may arise include ischemia (Ratnayake et al., 2018), anemia (Odinaka et al., 2015), thrombosis, hemolysis (Akyıldız et al., 2016; França et al., 1994; Toledo et al., 2018; Witharana et al., 2021), disseminated intravascular coagulation (DIC) (França et al., 1994), and shock (Azevedo et al., 2006; Babikir et al., 2021b; França et al., 1994; Mendonça-da-Silva et al., 2021; Rauf et al., 2021), which may subsequently lead to hypovolemia (Ruwanpathirana and Priyankara, 2022; Silva Junior et al., 2017).

Anaphylactic shock is an IgE-mediated immune system response resulting in hypoperfusion and vasodilation (Ediger et al., 2018). It usually occurs in individuals who have already suffered a bee sting or in people with allergies. This reaction can lead to mortality and organ damage. Another immune system response is mast cell activation syndrome, characterized by an excessive production of mast cells. The inflammatory effects of the venom can trigger multisystem complications, resulting in multiple organ damage and failure (Ruwanpathirana and Priyankara, 2022). Rhabdomyolysis, a condition characterized by the rupture of skeletal muscle cells, is strongly linked to bee stings envenoming, potentially contributing to the development of acute kidney injury (AKI) (Mendonça-da-Silva et al., 2021; Silva Junior et al., 2017). Other complication of the muscular system is hemiparesis, a common condition characterized by muscle weakness after an ischemic stroke, which can lead to immobilization or a decrease in the victim's physical activity. (Wist et al., 2016).

These outcomes are largely contingent upon factors such as the

number of stings, the patient's age, weight, existing health conditions, and medical interventions (Barbosa et al., 2017; Pucca et al., 2019b). However, we do not have specific diagnoses or laboratory protocols for monitoring the clinical evolution of patients. Although it is easy to diagnose, honeybee sting envenoming are difficult to monitor, and require different laboratory tests such as fibrinogen, APTT, PT and D-dimer assay for diagnosis and monitoring of disseminated intravascular coagulopathy, blood complete count to identify internal hemorrhages and hemolytic anemia (evidenced by the drop in red blood cells and hemoglobin levels; elevated serum concentrations of CK, myoglobin, lactate dehydrogenase (LDH), potassium, creatinine, and aspartate aminotransferase (AST) for rhabdomyolysis; gamma GT, alkaline phosphatase, alanine aminotransferase (ALT) and AST for identification of liver injury; urea, creatinine, sodium, potassium for assessment of kidney damage. In addition, clinical complications such as cerebral venous thrombosis, subarachnoid hemorrhage, acute limb ischemia, acute cerebellar infarction, and others have been commonly reported. Diagnosis for these cases includes continuous physical examination and use of tests such as magnetic resonance imaging, and computed tomography, use of duplex ultrasound, computed tomography angiography, and magnetic resonance angiography, and invasive angiogram (Table 1).

In the multicenter phase I/II clinical trial of antivenom for the treatment of Africanized bee stings (Oliveira et al., 2024), several clinical and biochemical parameters were considered for monitoring envenoming and therapeutic success (Barbosa et al., 2017, 2021). With that, it became clear the need is major to development of methods to quantify the venom in blood plasma of victim, which would assist in the quantification of the residual venom that is slowly released into the bloodstream. Under these conditions, the renewal of antivenom serum administration needs to be planned based on the half-life of F $(ab')^2$, and on the amount of bee venom in circulation, which is more difficult to determine, with the need to methods that can monitor the abundance of toxins released into the circulation.

5. Spider bites

The epidemiological impact of spider bite envenoming is complicated by various factors, including challenges in distinguishing lesions, identifying suspected spider species, determining the specific causative spider, and the potential for imprecise identification by professionals (Diaz, 2004; Lopes et al., 2020). Regrettably, accurate diagnoses often rely on patients bringing the spider to the hospital, increasing the likelihood of precise identification. In most cases, diagnoses remain presumptive or uncertain. The challenge escalates when patients do not feel or see the spider, relying solely on clinical and laboratory assessments, along with knowledge about the regional species distribution, for diagnosis (Vetter and Isbister, 2008).

Diagnosis considering systemic and/or local symptoms is difficult, as they are not specific and can be confused with other medical conditions that have been or can be diagnosed as bites by other animals. The diagnosis is basically clinical and focused on the skin wound; however, the clinical team also uses laboratory tests, although nonspecific, to obtain a possible differential diagnosis (Dunbar et al., 2022; Jerusalem and Salavert Lletí, 2018; Langner et al., 2021). The most common blood tests are hematological tests, hemostatic tests, and biochemical tests (Loden et al., 2020). Laboratory diagnosis depends on the presence of several hematological tests (analysis of the red series and WBC) to identify hemolysis and leukocytosis, hemostatic tests (fibrinogen, APTT, PT and D-dimer assay) to assess the presence of disseminated intravascular coagulopathy for directing the diagnosis.

Faced with different confounding factors in the clinic, many cases of spider bites are neglected, causing the clinical condition to evolve from mild to moderate, which can result in tissue loss and death (Danilo Leite da Silva et al., 2021; Rosen et al., 2012). In spider bite by *Loxosceles*, the development of systemic loxoscelism is common, and presents a wide variety of clinical manifestations, such as intravascular hemolysis and hemolytic anemia, renal failure, hemostatic changes, cerebral, cardiac, hepatic disorders, and others (Gremski et al., 2022).

Hemolysis is diagnosed mainly by laboratory tests that include Hemoglobinuria; low hematocrit; direct Coombs positive; Anemia; positive DAT 1; Anemia; hematuria; Low hemoglobin; increased LDH 2; indirect bilirubin; abnormal coagulation profile; myoglobinuria; increased whole blood, C-protein reactive, reticulocytosis, increased whole blood lactate (Calhoun et al., 2022; Harry et al., 2022; Lane et al., 2011; Nance, 1961). Furthermore, clinical manifestations such as fever, jaundice, dark urine, malaise, pallor, rash, fatigue, exanthem, low oxygen saturation, nausea, abdominal pain, vomiting, dyspnea, body aches, bilateral scleral icterus are reported in different frequencies of patients who develop hemolysis.

Cases of systemic loxoscelism with acute renal failure have been reported in patients of all ages, especially in pediatric cases (Gremski et al., 2022). Diagnosis begins with clinical signs of impaired renal function and laboratory tests. Clinical signs are generally oliguria, vomiting, jaundice, fever, hemolysis, hemolytic anemia, rhabdomyolysis, hypotension, fatigue, dark urine, malaise, periumbilical pain, headache, nausea, and tachycardia. From the perspective of laboratory tests, increased levels of urea, potassium and creatinine in the blood, proteinuria, hematuria, pyuria, heterogeneous enhancement pattern of kidneys found in tomography of the abdomen and pelvis are commonly reported (Albuquerque et al., 2018; Anwar et al., 2013; de Siqueira França et al., 2002; Golay et al., 2013; Hubbard and James, 2011; Nguyen and Pandey, 2019; Rosen et al., 2012).

Pain, and radiating spasms and pain, blurred vision, tachycardia, poor peripheral perfusion, prostation, pallor, cyanosis, diaphoresis, tremors, dyspnea, and pulmonary edema are clinical manifestations commonly reported in cases of spider veins envenoming by *Phoneutria*, assist to diagnosis and discrimination among other accident-causing spiders. In addition, laboratory tests based on blood analysis are little used for diagnostic and monitoring purposes (Bucaretchi et al., 2016). In more serious cases, local clinical complications such as Raynaud's phenomenon may occur due to compromised blood flow caused by edema, causing a sensation of cold and pale blue coloration. However, no laboratory tests have yet been reported that could be used for identification of Raynaud's phenomenon, although aortography, arteriography, venous and arterial duplex ultrasound can be used to rule out the presence of thrombosis (Salvatierra and Ramos, 2018).

Latrodectism cases present on physical examination intense muscle pain and stiffness, muscle spasms, agitation, petechiae, grunting respirations, priapism and generalized tremors, peripheral cyanosis, a third cardiac sound, crackles over both lung fields, and a rigid, board-like abdomen (Emara et al., 2022; Friedman et al., 2021; Pneumatikos et al., 2003). Laboratory tests may show leukocytosis, increased platelet count, tendency to increase creatine kinase, increased levels of lactate dehydrogenase, and increased levels of aspartate aminotransferase (Emara et al., 2022; Friedman et al., 2021; Pneumatikos et al., 2003). Furthermore, the venom can cause dilation of the heart chambers and severe global hypokinesia of the left ventricular wall, making it necessary to perform an echocardiogram for evaluation (Pneumatikos et al., 2003). Furthermore, it is recommended to perform electrocardiogram to evaluate the presence of ST elevation in leads I and aVL with reciprocal ST segment depression in infero-lateral leads with elevated cardiac biomarkers (CK-MB, and cTnI) (Emara et al., 2022).

The bulk of studies focusing on tools to identify and quantify toxins are centered around *Loxosceles* sp. These studies utilize diverse samples like skin exudates (through passive hemagglutination inhibition test and ELISA) (Barrett et al., 1989; Keklikci et al., 2008; Krywko and Gomez, 2002; McGlasson et al., 2009; Stoecker et al., 2006), biopsy and hair samples (employing competitive ELISA) (Gomez et al., 2001; Krywko and Gomez, 2002; Miller et al., 2016), and serum (Barbaro et al., 1992; Chávez-Olórtegui et al., 1994, 2001), all for detecting *Loxosceles* venom via ELISA. Despite reports of *Loxosceles* venom detection for a considerable time, its practical use in clinical settings remains unclear.

Table 1
Complications associated with honeybee stings envenoming.

System/Organ	Clinical complications	Diagnostic	Ref.
Cardiovascular	Acute myocardial ischemia	Electrocardiogram	(Pirasath et al., 2021; Sheshala et al., 2021)
	Acute myocardial injury	Change in plasma cardiac troponin (cTn) and change in electrocardiogram	Bindu et al. (2013)
	Kounis syndrome (KS)	Eosinophils count, cardiac enzymes (CK, CK-MB) and troponin I or T, C-reactive protein, total and specific immunoglobulin E (IgE) Histamine, chymase, serum tryptase levels and arachidonic acid products.	(Acehan et al., 2022; Aytekin et al., 2020; E Khoda et al., 2023; Gopinath et al., 2022; Kamalesh et al., 2023; Katsanou et al., 2018; Thwe et al., 2022; Tsuruta et al., 2022)
	Left ventricular hypertrophy/ Left ventricular systolic dysfunction	Echocardiography, cardiovascular magnetic resonance imaging (MRI) and scintigraphy	(du Toit-Prinsloo et al., 2016)
	Mobitz type 2 heart block	Change in plasma CK-Mb, cardiac troponin (cTn) and change in electrocardiogram	Chaudry (2020)
	Myocardial damage	Cardiac enzymes (CK, CK-MB) and troponin I or T	(França et al., 1994; Su et al., 2021)
	Pericardial effusion	Chest X-ray, electrocardiogram, transthoracic echocardiography, computed tomography scan, cardiac magnetic resonance imaging, and pericardiocentesis.	Azevedo et al. (2006)
Digestory	Boerhaave's syndrome	Chest radiology examination	Sheshala et al. (2021)
	Gastrointestinal hemorrhage	Serum liver enzymes (AST, ALT, GGT) and abnormal coagulation tests (PTT and APTT)	(Mellyana et al., 2019; Önder and Aktan, 2021)
Hematologic	Acute limb ischemia	Examination with Doppler ultrasound, Computed Tomography Angiography, and Magnetic Resonance Angiography, and Invasive Angiogram	Ratnayake et al. (2018)
	Acute femoral thrombosis	Magnetic resonance imaging (MRI)	Ratnayake et al. (2018)
	Anemia	Reed blood cells count and levels of hemoglobin	Odinaka et al. (2015)
	Brachial artery thrombosis	Digital angiography	Akgul and Bagırov (2021)
	Deep vein thrombosis (DVT)	Doppler ultrasonography (USG)	Cil et al. (2022)
	Disseminated intravascular coagulation	Attention to hemostatic parameters and management of the underlying disease	França et al., 1994
	Thrombotic microangiopathy	Blood picture examination (polychromatic cells, ovalocytes, and schistocytes)	Witharana et al. (2021)
	Thrombotic thrombocytopenic purpura (TTP)	Platelets count	Khalighi et al. (2020)
	Hepatic dysfunction/Ischemic hepatitis	Increase of levels of gamma GT, alkaline phosphatase, ALT, AST, and Bilirubin	(Farhat et al., 2018; França et al., 1994; Toledo et al., 2018)
	Rhabdomyolysis	Monitoring laboratory tests and physical examination: elevated serum concentrations of CK (>5 × the upper limit of normal or >1000 IU/L), myoglobin, lactate dehydrogenase, potassium, creatinine, and aspartate aminotransferase (AST)	(Betten et al., 2006; Constantino et al., 2020; França et al., 1994; Geoffroy et al., 2021; Hiran et al., 1994; Jain et al., 2012; Mendonça-da-Silva et al., 2021; Rauf et al., 2021; S et al., 2020; Seelarathna et al., 2020; Toledo et al., 2018)
Nervous	Acute bilateral cerebellar infarction	Continuous physical examination and use of tests such as magnetic resonance imaging and computed tomography	Mahale et al. (2016)
	Axonal motor polyneuropathy	Electrophysiological nerve studies	(Poddar et al., 2012; Saini et al., 2014)
	Cavernous sinus thrombosis	Magnetic resonance	Walter et al. (2020)
	Encephalitis	Electroencephalography	Önder and Aktan (2021)
	Hemorrhagic/Ischemic stroke	Use of imaging exams, such as magnetic resonance imaging, and computed tomography for support	(Abhishek et al., 2021; Akyıldız et al., 2016; Babikir et al., 2021b; Gupta, 2019; Jain et al., 2012; Kabra et al., 2022; Ramlackhansingh and Seecheran, 2020; Rathnayaka et al., 2021; Varuni et al., 2018)
	Multiple acute cerebral infarcts	Computed tomography	(Gupta, 2019; Jain et al., 2012; Walter et al., 2020)
	Subarachnoid hemorrhage	Computed tomography, and pay attention to erythrocytes count	(du Toit-Prinsloo et al., 2016; Gupta, 2019; Oliveira et al., 2000)
Renal	Acute kidney injury	Assess the need for renal replacement therapy, presence of hypervolemia with pulmonary edema, severe hyperkalemia, among others	(Betten et al., 2006; Constantino et al., 2020; Mellyana et al., 2019; Pirasath et al., 2021; Rauf et al., 2021; Ryakitimbo et al., 2018; S et al., 2020; Toledo et al., 2018; Walter et al., 2020; Witharana et al., 2021)
	Acute kidney failure	Assess the need for renal replacement therapy, presence of hypervolemia with pulmonary edema, severe hyperkalemia, among others	(Akyıldız et al., 2016; Babikir et al., 2021b; França et al., 1994; Geoffroy et al., 2021; Hiran et al., 1994; Jain et al., 2012; Mendonça-da-Silva et al., 2021; Sunny and Abrencillo, 2021)
Respiratory	Acute pulmonary emphysema	Objective examination (emphysematous chest) and radiology examination (chest x-ray), however it is based on high-resolution computed tomography (HRCT) of the lung	Mondello et al. (2023)
	Acute respiratory distress syndrome (ARDS)	Pulse oximetry, chest x-rays, blood gas analysis and end-tidal carbon dioxide monitoring (capnometry)	(Akyıldız et al., 2016; Azevedo et al., 2006; E Khoda et al., 2023 França et al., 1994; Mendonça-da-Silva et al., 2021; Rauf et al., 2021; Singer and Lande, 2022)
	Bronchial obstruction	Chest x-ray and pulmonary function tests	Mondello et al. (2023)
	Pulmonary congestion	Physical examination, chest x-ray and lung ultrasound	(Mondello et al., 2023; Riches et al., 2002; Silva et al., 2013)
	Pulmonary edema	Chest x-ray	(Azevedo et al., 2006; Mellyana et al., 2019; Mondello et al., 2023; Riches et al., 2002; Seecheran et al., 2021)
	Pulmonary hemorrhage	Chest x-ray and bronchoalveolar lavage	Mondello et al. (2023)

Consequently, a pressing need for studies showcasing the efficacy of these kits in routine laboratory-hospital practices. On the other hand, to identify and quantify the venoms of spiders of the genus *Phoneutria*, *Atrax,* and *Hadronyche*, only serum samples were inspected, unlike *Loxosceles*. Although serum is a widely collected sample in the clinic, experimental and clinical loxoscelism models were unable to detect circulating venom, probably because of its concentration at the bite site (Krywko and Gomez, 2002; Stoecker et al., 2006). On the other hand, as *Phoneutria*, *Atrax,* and *Hadronyche* venoms exhibit a systemic toxicity profile, detection of the venom in serum samples was possible (Bucaretchi et al., 2008; Chávez-Olórtegui et al., 2001; Lucas, 1988; Miller et al., 2016).

6. Diagnostic tests: from the bench to the hospital bed

The analysis of changes in the blood-plasma proteome because of envenomings by venomous animals is certainly informative for researchers studying the pathogenesis of diseases and host immune responses or interested in identifying diagnostic or prognostic biomarkers aiming to identify endogenous candidates, as well as performing traceability of toxins (Cavalcante et al., 2023a,b). This could be translated to the clinic through the development of more simplified diagnostic tools, based on targets identified by mass spectrometry. Biomarkers are indicator biomolecules that aid in early diagnosis, discriminate between different diseases, and provide valuable tools to monitor disease progression/severity (García-Gutiérrez et al., 2020; Kamtchum-Tatuene and Jickling, 2019; Manole et al., 2019; Mohammed et al., 2022; Shu et al., 2020).

Although existing diagnostic approaches (including analysis of clinical symptoms, identification of the animal causing envenoming, laboratory diagnostic methods including hematology and biochemistry, and the use of diagnostic imaging tools) that are generally implemented clinically, they are not robust and sensitive and have low predictive potential. Furthermore, existing routine detection techniques are unable to provide any prognostic information regarding envenoming, or to clearly discriminate between envenoming that have overlapping clinical manifestations. To this end, protein markers are potential candidates for the development of alternative diagnostic and prognostic approaches, but to achieve this, studies must follow the validation workflow, from bench to patient. Thus, although several diagnostic and monitoring tests are in development, their reports present fragments of results from the stages that reflect the iterative nature of translational research (Keim-Malpass et al., 2023; Seyhan, 2019) and failure to establish key development steps returns test evaluation to a previous phase and potential test redesign, as well as moving forward to the next phase (Leeflang and Allerberger, 2019).

Many reports have addressed the path to be taken by a candidate molecule for a new drug, from the bench to the target population (Lombardino and Lowe, 2004). However, there are few studies that focus on the translational path of testing for diagnosis and monitoring. Therefore, the development of a new diagnostic test must follow at least five phases (Fig. 2): (i) test selection and initial measurements of single test performance, (ii) clinical test performance measurements, (iii) impact on clinical decision-making and health outcomes, (iv) effectiveness of the new diagnostic strategy on clinical outcomes, and finally, (v) implementation and effects at the health system and population level (Leeflang and Allerberger, 2019; Walter et al., 2019). Many reports have addressed the path to be taken by a candidate molecule for a new drug, from the bench to the target population.

7. Perspectives

In the future, diagnostic tools for venomous animal identification post-accidents are likely to advance significantly, driven by innovative technologies and biomarker discoveries. Precision in identification could arise from enhanced proteomic analyses, allowing for rapid, species-specific identification of venomous animals involved in envenoming incidents. Biomarkers signaling poor prognosis or worsening

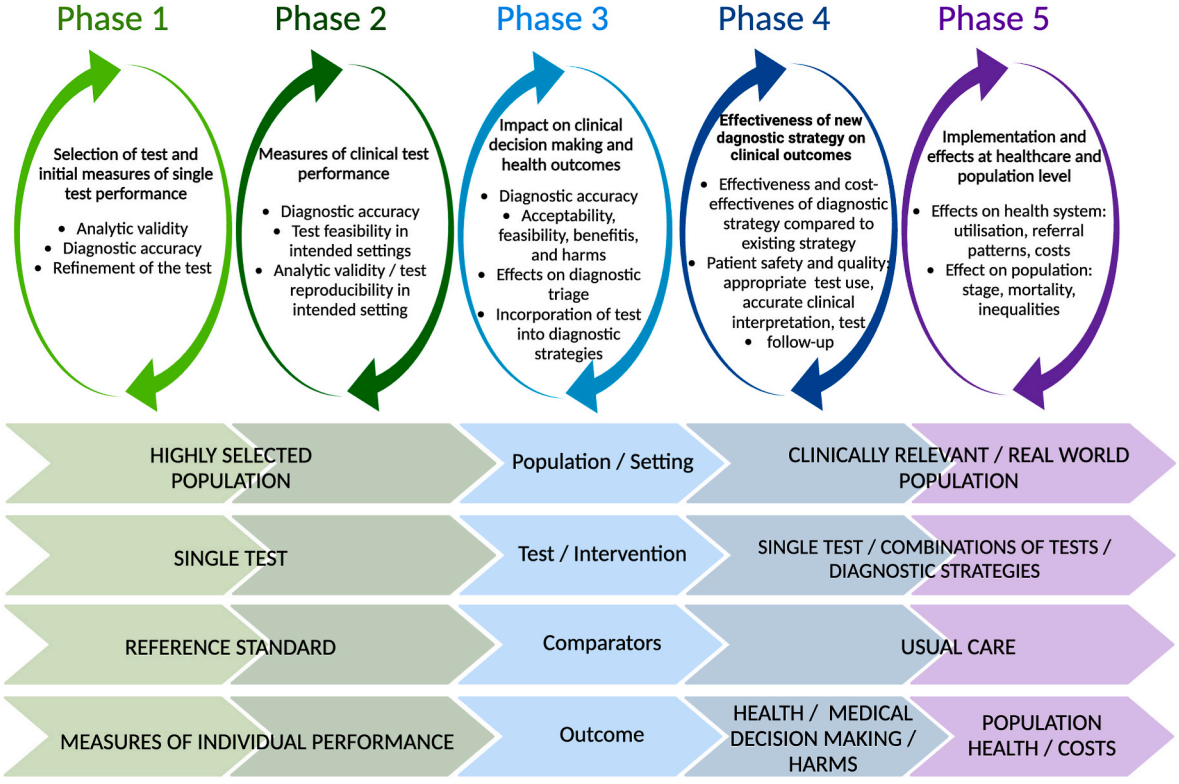

Fig. 2. Journey to cross the valley of death in the development of new disruptive technologies for the diagnosis and monitoring of patients victims of snakebites envenoming.

conditions may become pivotal in guiding treatment decisions. Sophisticated diagnostic assays might be developed to detect these prognostic indicators, enabling early intervention strategies and personalized treatment plans. The integration of artificial intelligence and machine learning could streamline diagnostic processes, improving accuracy and aiding in the prediction of clinical outcomes following envenoming incidents. Collaborative efforts among researchers, healthcare professionals, and technology experts will likely play a crucial role in realizing these advancements, ultimately enhancing patient care and outcomes in cases of venomous animal envenoming.

CRediT authorship contribution statement

Joeliton S. Cavalcante: Writing – original draft, Validation, Conceptualization. **Sabrina Santana Toledo Arruda:** Writing – review & editing, Visualization, Investigation. **Pedro Marques Riciopo:** Writing – original draft, Methodology, Data curation. **Manuela Pucca:** Writing – review & editing, Writing – original draft, Conceptualization. **Rui Seabra Ferreira Junior:** Writing – review & editing, Visualization, Supervision.

Ethical statement

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data that has been used is confidential.

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