Diagnostic Challenges in the Emergency Setting

Doctoral (Ph.D.) thesis

Csaba Varga M.D.

University of Pécs Faculty of Health Sciences

Doctoral School of Health Sciences

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UNIVERSITY OF PÉCS FACULTY OF HEALTH SCIENCES

DOCTORAL SCHOOL OF HEALTH SCIENCES

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Associate-supervisor: Prof. Dr. Tibor Oláh

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1 Abbreviations and glossary

ACE-I: angiotensin concerting enzyme inhibitors

ACh: acetylcholine

AChEis: acetyl choline esterase inhibitors

AF: atrial fibrillation

ARB: angiotensin II receptor antagonists

CKD: chronic kidney disease

CPR: cardiopulmonary resuscitation

DM: diabetes mellitus

ECG: electrocardiogram

ER: Emergency Room

ESRD: end-stage renal disease

HF: heart failure

HT: hypertension

K suppl: potassium supplementation

nAChRs: nicotinic acetylcholine receptors

OHCA: out-of-hospital cardiac arrest

PLA2: Phospholipase A2

RRT: renal replacement therapy

SfEMG: single-fiber electromyography

V.b.berus: Vipera berus berus

V.b.bosniensis: Vipera berus bosniensis

VF: ventricular fibrillation

VT: ventricular tachycardia

2   Introduction

2.1   The special features of Emergency Care

Healthcare professionals working in the prehospital emergency setting as well as in the Emergency Room (ER) face a multitude of challenges. They are required to diagnose and initiate treatment encompassing a wide range of diseases involving critical thinking and be knowledgeable in various areas of the medical field.

The goal of care in the area of Emergency medicine is to treat illnesses which develop within a short time-frame and which without adequate treatment could lead to negative long-term outcomes for the patients, independent of the patients' other comorbidities. According to the European Society for Emergency Medicine, time-dependency, allocation of resources and integration into care, epitomize the root principles of Emergency medicine (1). Within the context of providing modern, acute care vulnerable patients are identified and treated based on the severity of their condition in a place where adequate resources for the treatment are readily accessible. Providing optimal, personalized therapy tailored to the patients' needs is a key feature of this form of medical approach. It also follows, from the underlying principles that time is of the essence when providing Emergency care.

Setting up a timely, accurate diagnosis is essential and failure to do so may have fatal consequences. If a patient is in cardiac arrest, cardiopulmonary resuscitation (CPR) needs to be initiated immediately and the underlying reasons for cardiac arrest concomitantly detected and treated for the optimal short and long-term outcome of the patient (2). Uncovering the cause of a life-threatening medical condition, with limited time available for doing so and often with limited resources and diagnostic tools in the prehospital emergency setting is often a demanding task (3, 4).

On the other hand, even when setting up a diagnosis appears straightforward, physicians at the ER are often faced with the difficulties of interpreting variations in the symptoms caused by the hypothesized illness. In most patients presenting to the ER, common diseases are efficiently recognized and treated based on international guidelines. However, providing care for patients can be challenging when patients with less frequent diseases are admitted to the ER or when evidence regarding the medical condition is lacking.

This thesis includes two important studies, which at first may appear to have little in common. However, the focuses of both studies depict the diverse diagnostic and therapeutic challenges within emergency care. In the first study, the role of the electrocardiogram (ECG) in hyperkalemia is investigated. Then, a unique case of snakebite is reported, where the patient's symptoms and medical findings are described

The choice of topics unequivocally shows the difficulties inherent in Emergency Care. Common and/or potentially life-threatening medical conditions, such as hyperkalemia in our study, must be recognized and treated as soon as possible, and evidence-based step-by-step protocols are available for the treatment of this condition. The use of ECG as a simple tool for the prompt diagnosis of this electrolyte disorder appears attractive however, medical professionals must be aware of its limitations. By gathering data regarding the role of the ECG in setting up a diagnosis in hyperkalemic and normokalemic patients, we aimed to help the work of health care professionals in the prehospital and hospital emergency setting. This is particularly important in cases when a patient develops life-threatening arrhythmia and laboratory test results are not immediately available. The physician is then confronted with the difficulty of deciding whether to treat a suspected hyperkalemia, even if he or she is fully aware of the pertaining guidelines.

Although guidelines provide considerable assistance in the treatment of common diseases and - in some instances- in rare medical conditions as well, adequate information regarding the treatment of rare medical conditions, such as snake envenoming by certain species may be lacking or may not be valid in some individual cases. In such instances, the emergency physician is required to follow protocols for the specific treatment of the snake envenoming but the ability to provide personalized care based on the unfolding symptomatology is also essential for achieving the most optimal results. The significance of case reports within all medical fields is unquestionable because they describe the special aspects and treatment options of conditions, where guidelines cannot be followed for one or more of the reasons described above. Therefore, we found it important to describe the rare case of a snake envenoming by the *Vipera berus bosniensis*, thereby adding valuable information to the limited data currently available in the literature.

Thus, the thesis handles one common and one rare medical condition, such as hyperkalemia and snake envenoming, which are excellent reflections of the variety of challenges health care professionals face in Emergency Care.

2.2   Importance of hyperkalemia in emergency care

Over half of all cardiovascular deaths are due to sudden death, with the cause being sudden cardiac arrest and taking place as out-of-hospital cardiac arrest (OHCA) (5). Sudden cardiac arrest has a multifactorial background and is usually preceded by ventricular tachycardia (VT) or (VF) (6). Mortality from sudden cardiac arrest affects over 400 000 people in Europe each year (7). Risk factors of cardiac arrest include heart disease, such as coronary heart disease and congestive heart failure, diabetes mellitus, inherited factors and electrolyte imbalances (5).

According to the European Resuscitation Council, independent of the underlying reason for cardiac arrest, the essential primary interventions include early recognition of the condition, calling for help, early defibrillation, high-quality cardiopulmonary resuscitation and the treatment of reversible causes (2). In periarrest situations and during resuscitation it is essential to rule out reversible causes, such as the '4 Hs and 4 Ts', indicating Hypoxia, Hypo/Hyperkalemia and other electrolyte disorders, Hypo/Hyperthermia, Hypovolemia, and Tension pneumothorax, Tamponade (cardiac), Thrombosis and Toxins (poisoning) (2).

From these, hyperkalemia, a relatively common condition, may lead to fatal cardiac arrythmias. The incidence of hyperkalemia in hospitalized patients is relatively high and varies between 1.1 and 10 % (8-10). Therefore, electrolyte disturbances should be suspected in patients at risk, with comorbidities, such as diabetes mellitus and cardiac or renal failure. Based on the 2015 guidelines of European Resuscitation Council, electrolyte disturbances, such as hypo- and hyperkalemia should be corrected preferably before cardiac arrest happens (2)**.** Although, portable devices are readily accessible in prehospital care to measure temperature, oxygen saturation and blood glucose levels, the diagnosis of hyperkalemia in prehospital settings is currently not possible. Since alterations in the ECG-s of patients with hyperkalemia have been documented in a number of investigations, ECG-s have been suggested to facilitate a non-invasive approach to diagnosing hyperkalemia (11)**.**

2.3 Symptoms and causes of hyperkalemia

The complaints, symptoms and physical findings of hyperkalemia are non-specific. They may include symptoms such as abdominal pain, nausea, vomiting, weakness, muscle twitching, paraesthesia, paralysis, dysathria, and dysphagia (12, 13). Physical findings of arrythmia, hypotension and respiratory or cardiac arrest may be observed in patients with hyperkalemia (12, 13).

The causes of hyperkalemia are multifactorial and encompass a wide range of medical conditions. The main reasons underlying hyperkalemia include, renal failure (acute and chronic kidney disease), drugs (angiotensin concerting enzyme inhibitors (ACE-I), angiotensin II receptor antagonists (ARB), beta-blockers, potassium-sparing diuretics and non-steroidal anti-inflammatory drugs), metabolic acidosis, endocrine disorders (for e.g. Addison's disease), inappropriate diet (particularly in patients with chronic kidney disease), conditions with tissue breakdown (e.g. tumor lysis, rhabdomyolysis, haemolysis) and spurious (pseudo-hyperkalemia) (2, 14). Medications often associated with hyperkalemia are shown in *Table 1*.

Medications associated with hyperkalemia

The following medications contribute to the development of hyperkalemia:

- Heparin
- Calcineurin inhibitors
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers
- Nonsteroidal anti-inflammatory drugs
- Potassium-sparing diuretics
- Trimethoprim
- Pentamidine

Table 1 Adapted from: Runner's new diet, his collapse, and his ECG: when a rapid ECG diagnosis can save the day by Ringer M, Pulfrey S, Can Fam Physician. 2014 Apr;60(4):340-4.

2.4   ECG alterations caused by hyperkalemia

The concentration of potassium in the serum is tightly regulated between 3.5 and 5.5 mmol/l. Potassium levels are considered elevated above 5.5 mmol/l (15). However, there is no exact definition of hyperkalemia, because the occurance of symptoms associated with hyperkalemia gradually increases with the elevation of serum potassium levels. Severe hyperkalemia is generally defined as a serum potassium level above 6.5 mmol/l -7 mmol/l (15, 16).

The concentration gradient of potassium existing between intracellular end extracellular fluid compartments enhances the excitability of nerve and muscle cells, including in those of the heart. The pH of the serum affects potassium levels. In alkalaemia potassium flows from the vascular to the cellular space, while in acidaemia the potassium moves in the opposite direction (2). Elevated serum potassium levels induce a lowering of the resting membrane potential, slowing of the velocity of phase 0 of the action potential, which in turn leads to the slowing of conduction (17). Meanwhile, the transmembrane potassium permeability increases, which raises the action potential's phase 3 velocity, thus decreasing the length of the action potential (17). The characteristic ECG changes of hyperkalemia reflect these electrophysiological effects (18). Patients with end-stage renal disease (ESRD) have been thought to develop a tolerance for hyperkalemia, which results in that the commonly observed cardiac and neuromuscular sequence of symptoms present in patients with normal renal function are not visible in ESRD patients (19, 20).

As the level of serum potassium increases, typical ECG alterations appear in a characteristic sequence (16). Mildly elevated potassium levels (5.2-5.9 mmol/l) may cause tall T waves or peaked/tented T waves (16). These are often described as symmetrically narrow, though the deflection is often wide and of large amplitude (16). Although tall, "hyperacute" T-waves are a sign of acute myocardial ischemia and can be mistaken for the peaked T-waves of hyperkalemia, peaked hyperkalemic T-waves tend to be narrow with a prominent or sharp apex (21). Furthermore, pseudonormalization of inverted T waves associated with left ventricular hypertrophy can occur (22). The acceleration of the terminal phase of repolarization is often responsible for these T wave alterations and can best be detected in the precordial leads (16). As the level of serum potassium rises further, cardiac conduction between heart muscle cells is repressed. The cellular action potential is decreased through the inactivation of the sodium channel (16). Moderately elevated potassium levels (6.0-7.0

mmol/l) typically result in PR interval prolongation, decreased P wave amplitude, disappearance of the P wave, widening of the QRS complex or conduction blocks with escape beats and the loss of the P wave (16). Since atrial tissue is more sensitive to potassium level changes P wave flattening and PR interval prolongation are generally visible prior to the prolongation of the QRS interval. The QRS complex in hyperkalemia may liken the appearance of a right or left bundle branch block alteration, except the conduction delay is seen throughout the QRS complex, and not just in the initial or terminal parts of the complex, as is visible in bundle branch block (23). Bypass tracts are also more sensitive to delayed conduction due to increasing potassium levels, which can lead to the normalization of the ECG in patients with Wolff-Parkinson-White syndrome (16). In severe hyperkalemia (>7.0 mmol/l) a markedly prolonged and wide QRS can fuse with the T-wave, causing a "sine-wave" appearance on the ECG, which can induce a fatal event such as ventricular fibrillation and asystole (16). As described in previous reports, however, metabolic changes, such as hypernatraemia or hypercalcaemia can diminish the transmembrane effects of hyperkalemia, so as to make the ECG changes suggestive of hyperkalemia less apparent (24).

2.5 Treatment of hyperkalemia in adults

The main focus of the treatment of life-threatening hyperkalemia is to block the effects of potassium on myocyte transmembrane potential and cardiac conduction and to decrease the level of extracellular potassium (16). If the patient with hyperkalemia is not in cardiac arrest, the patient should be assessed according to the ABCDE approach, intravenous access obtained, serum potassium checked and a 12-lead ECG recorded. Cardiac rhythm should be monitored in patients with severe hyperkalemia (2). Treatment should be initiated according to the hyperkalemia emergency treatment algorithm, as shown in *Figure 1*.

According to the European Resuscitation Council Guidelines for Resuscitation 2015 the treatment of hyperkalaemia, depends on the severity of hyperkalemia, and should be initiated according to the following protocol (2):

Mild elevation (5.5–5.9 mmol L−1). (2):

• Address cause of hyperkalaemia to correct and avoid further rise in serum potassium (e.g. drugs, diet).

• If treatment is indicated, remove potassium from the body: potassium exchange resins-calcium resonium 15–30 g, or sodium polystyrene sulfonate (Kayexalate) 15–30 g, given either orally or by retention enema/PR (per rectum) (onset in >4 h).

Moderate elevation (6.0–6.4 mmol L−1) without ECG changes. (2):

• Shift potassium intracellularly with glucose/insulin: 10 units short-acting insulin and 25 g glucose IV over 15–30 min (onset in 15–30 min; maximal effect at 30–60 min; duration of action 4–6 h; monitor blood glucose).

• Remove potassium from the body (see above; consider dialysis guided by clinical setting)

Severe elevation (≥6.5 mmol L−1) without ECG changes. (2):

 • Seek expert help.

 • Give glucose/insulin (see above).

• Give salbutamol 10–20 mg nebulised (onset in 15–30 min; duration of action 4–6 h).

• Remove potassium from the body (consider dialysis).

Severe elevation (≥6.5 mmol L−1) with toxic ECG changes. (2):

• Seek expert help.

• Protect the heart with calcium chloride: 10 mL 10% calcium chloride IV over 2–5 min to antagonise the toxic effects of hyperkalaemia at the myocardial cell membrane. This protects the heart by reducing the risk of VF/pVT but does not lower serum potassium (onset in 1–3 min).

• Use shifting agents (glucose/insulin and salbutamol).

• Remove potassium from the body (consider dialysis at outset or if refractory to medical treatment)

Modifications to cardiopulmonary resuscitation. (2):

The following modifications to standard ALS guidelines are recommended in the presence of severe hyperkalaemia:

• Confirm hyperkalaemia using a blood gas analyser if available.

• Protect the heart: give 10 mL calcium chloride 10% IV by rapid bolus injection.

• Shift potassium into cells: Give glucose/insulin: 10 units shortacting insulin and 25 g glucose IV by rapid injection. Monitor blood glucose.

• Give sodium bicarbonate: 50 mmol IV by rapid injection (if severe acidosis or renal failure).

• Remove potassium from body: Consider dialysis for hyperkalaemic cardiac arrest resistant to medical treatment.

Consider use of a mechanical chest compression device if prolonged CPR is needed.

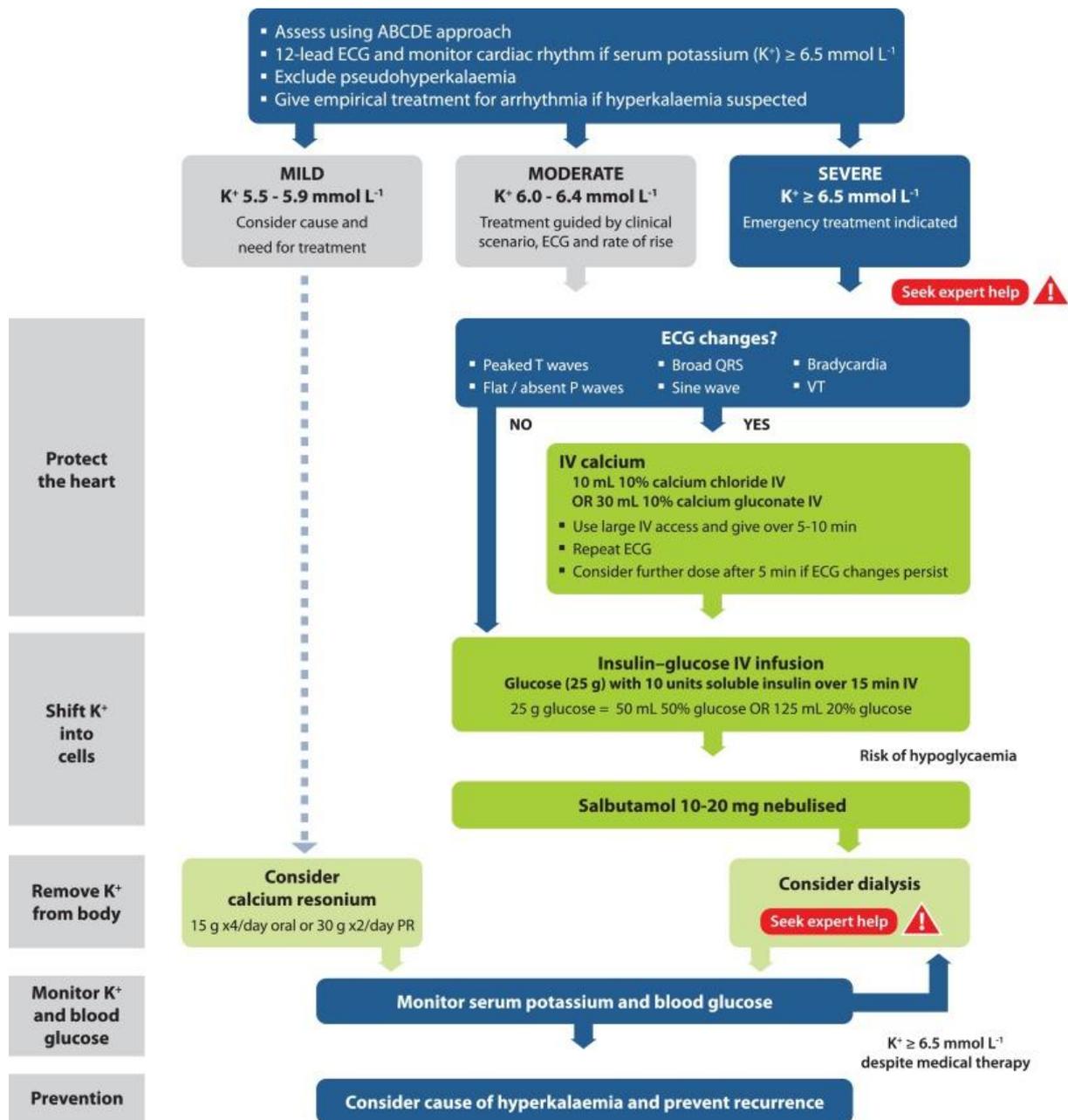*Figure 1: Emergency treatment of hyperkalemia. (PR: per rectum; VT: ventricular tachycardia)*

Reproduced with permission from the Renal Association and Resuscitation Council (UK).

Adapted from the European Resuscitation Council Guidelines for Resuscitation 2015 Section 4. Cardiac arrest in special circumstances by Truhlář A et al., Resuscitation. 2015 Oct;95:148-201. doi: 10.1016/j.resuscitation.2015.07.017. PMID: 26477412

2.6 Aims of the study regarding ECG alterations in hyperkalemia

Despite ECG manifestations considered typical for hyperkalemia, the clinical diagnosis of hyperkalemia remains difficult as the electrophysiological disturbances listed above are not pathognomic of potassium disorders nor do they appear in each patient with hyperkalemia (25). According to earlier studies, the prevalence of ECG alterations in hyperkalemia was as low as 14-59% of the cases (18, 25, 26). Reports about severe cases of hyperkalemia with none or minimal ECG alterations have also been published (18, 27).

A number of investigations have studied the correlation between elevated potassium levels and changes in the ECG (25, 26, 28). To our knowledge, however, no investigation has been conducted regarding the presence of ECG manifestations suggestive of hyperkalemia in patients with normal potassium levels.

The goal of our study was to compare the prevalence of ECG alterations suggestive of hyperkalemia in normokalemic and hyperkalemic patients. It was also our objective to examine the frequency of certain ECG alterations possibly associated with elevated potassium levels. By investigating the frequency of ECG changes in both groups of patients we aimed to elucidate whether these ECG alterations may facilitate recognition of hyperkalemia in the prehospital setting.

2.7 The medical relevance of snake envenomation

Throughout the world, hundreds of thousands of patients are affected by snakebite envenomation annually. Although snakebites are not as prevalent in Europe as in the sub-tropical and tropical regions of the world, certain snake subspecies of the genus *Vipera* account for serious envenomation and may lead to long-term consequences or even death in some patients (29). In Europe there are three species of venomous snakes categorized as medically important: *Vipera berus*, *Vipera aspis*, and *Vipera ammodytes*. *V. berus* is the most widespread species, present both in North-east and Central Europe. Clinically, *Vipera berus berus* and *Vipera aspis aspis* envenomations mostly cause local symptoms, but have been associated with causing systemic symptoms as well (hypotension, gastrointestinal and coagulation disorders, neurotoxicity) in cases of severe envenomation (30, 31)

2.8 The common adder (*Vipera berus*)

In Hungary, the common adder is the sole native venomous snake species of medical relevance. The lowland adder populations of Somogy County in South-Western Hungary are currently recognized as the Balkan or Bosnian adder, *V. b. bosniensis* (32). However, differences in the appearance between the nominate subspecies (*V. b. berus*) and the Bosnian subspecies, are not evident for laymen. Melanistic and very dark specimens can frequently be observed in these lowland adder populations (32, 33) *(Figure 2 A, B,C).*
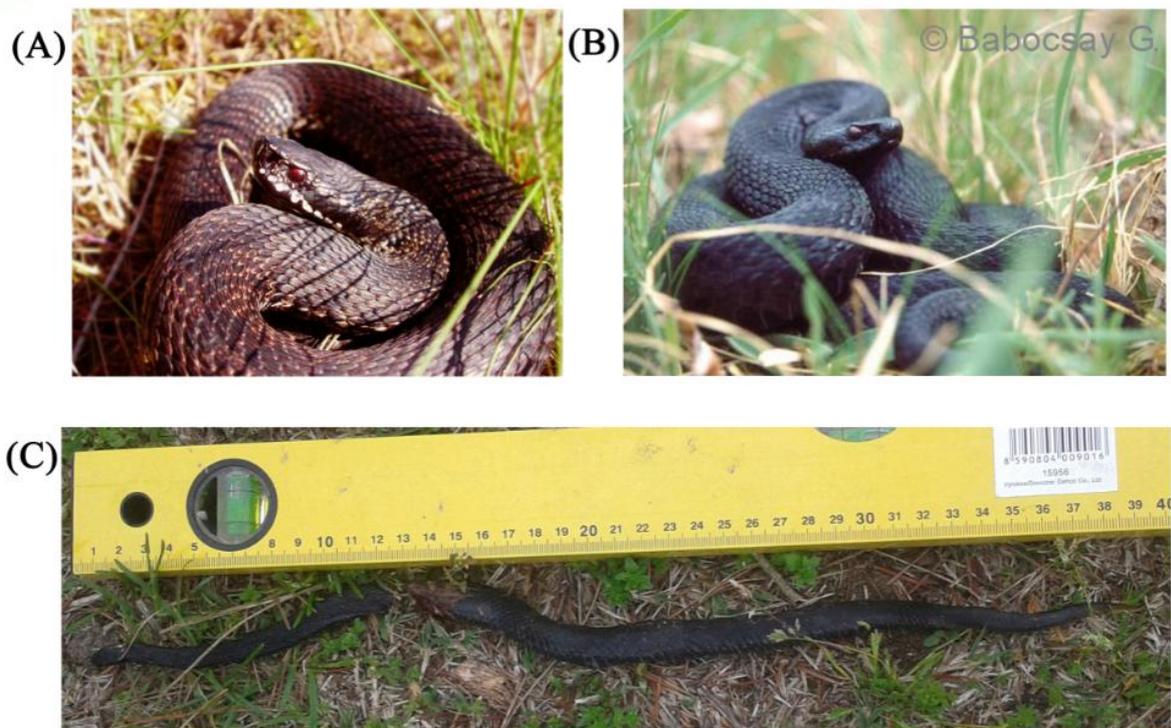
Figure 2. (A) A darkish coloured adult male specimen of V. b. bosniensis from Darvaspuszta. (B): A full melanistic V. b. bosniensis from Kaszo. (C): The culprit: a sub-adult melanistic specimen that caused the incident in Kaszo. (Photographs were taken by: (A) Tamas Malina; (B) Gergely Babocsay; (C) the patient.)

The first record of the occurrence of the adder in Somogy County dates back to the end of the 1920s. Specimens were collected in Kaszó by Dudich (34). Later Marián (35) thoroughly studied the geographical distribution range of *V. berus* populations in Somogy County during his field works. The earliest recorded snakebite accident caused by this taxon in this county was reported by Marián (33); the envenomed patient was transported to the Hospital of

Kaposvár in July 1951. In another historical case, a local forester was bitten by an adder near Homokszentgyörgy and the patient was admitted condition to the medical institute mentioned above in a critical, life-threatening condition (36).

In Central Europe, the common adder (*Vipera berus*) is ranked into category 2 based on its medical importance (37). According to the definition of WHO (2016) (37), the species belonging to this category are "*highly venomous snakes capable of causing morbidity, disability or death, but for which exact epidemiological or clinical data may be lacking and/or are less frequently implicated* (*due to their activity cycles, behaviour, habitat preferences or occurrence in areas remote to large human populations*)".

The common adder is considered a relatively small snake with an average length of 50-70 cm. The thick-set body of the snake ends in a short tail, with a dark zig-zag shaped streak a characteristical feature running across the length of the snake's back.*V. b. berus* is characterised by gender dichromatism, while *V.b. bosniensis* by its somewhat shorter length and lack of dichromatism. The snakes are generally brown in color, with a varying ratio of melanistic individuals. There are a relatively high number of dark, melanistic individuals in the South-Hungarian population of *V.b. bosniensis*. (38)

2.9   Envenoming by the common adder (*Vipera berus*). Symptoms.

Vipera berus envenomings are well documented in the medical and toxicology literature (39, 40). The purpose of snake venom is to enable the subduing and digesting of the prey. Venoms are made up of biologically active proteins: of synergistically functioning toxins and enzymes. There is a variation between the venom composition of individual snakes within the same species, which is heavily dependent on the snake population's geographic distribution (41). Certain signs and symptoms of envenomings are suggestive of this potential intraspecies venom variation – between different populations and at the intra-population level as well. The diversity of snake venom within a given species has previously been described in a number of reports, among members of the genus *Vipera* as well (41-43).

In a recent study, venom samples from several individual European adders (*Vipera berus berus*) within a defined population in Eastern Hungary were examined (44). Individual variations of venom components were identified and protease activity measured with

zymography (44). This showed that the protease activity constituting different venom patterns of the individuals were related to the adders' gender and age. The activity of the key component of venom neurotoxicity, Phospholipase A_2 (PLA2) activity of venoms was shown to be similar but not identical. The extracted venom samples differed in their neuromuscular paralysing effect on chick biventer cervicis nerve-muscle preparations (44). The report clearly demonstrated the individual venom variation among V. b. berus living in particular area of Eastern Hungary. (44) *Table 2* shows the list of case reports about neurotoxic envenoming by *V. b. berus* envenomings in the Carpathian basin.

Published case reports of neurotoxic envenomings by *V.b. berus* in the Carpathian basin.					
Author	Year of incident	Place of incident	Age of patient	Sex of patient	recorded carnival nerve disturbances
Blatt (1923)	1922	Transylvania	40 years	F	accomodation trouble, ophtalmoplegia, bilateral ptosis
Malina et al. (2008)*	1878	Western Transylvania	24 years	M	bilateral ptosis, blindness
Malina et al. (2008)**	1895	Western Transylvania	43 years	F	ophtalmoplegia
Malina et al. (2008)	2007	Eastern Hungary	27 years	M	diplopia, ophtalmiplegia
Gafencu et al. (2012) ⁂	not mentioned	South-Western Romania	14 years	F	blurred vision, bilateral ptosis, dysphagia
Malina et al. (2013)	2012	Eastern Hungary	12 years	F	bilateral but partial ptosis, gaze paresis, diplopia
Strugariu and Strugariu (2014)	2003-2011	North-Eastern Romania	9 years	F	bilateral ptosis

Table 2: List of case reports about neurotoxic envenoming by V. b. berus envenomings in the Carpathian basin.

Adapted from Individual variability of venom from the European adder (Vipera berus berus) from one locality in Eastern Hungary by Malina T et al., Toxicon. 2017 Sep 1;135:59-70.

Therefore, it is not surprising that occasionally relatively uncommon and/or atypical signs and symptoms develop in envenomed patients bitten by *V. berus* in different regions. The medical importance of this variability in venom composition is underlined by the observation that following snakebite patients may produce a wide range and severity of symptoms and therefore, need to be appropriately treated.

The bite of the common adder usually affects the limbs, with an equal number of bites having been reported on the upper as on the lower extremities (45). Two penetrating wounds are visible 3-10mm-s apart, indicating the imprint caused by the fangs. The ensuing edema of the area may hide these marks (38).

The typical symptoms of common adder envenomation initially include local symptoms. Following the needle-like sharp pain inflicted by the bite itself, envenomation causes a burning, then throbbing pain within minutes to half an hour of the bite. Local swelling and erythema generally ensue and the edema may reach its peak between 48-72 hours and gradually resolve within 2 weeks. In many but not all cases, the venom contains hemorrhagic toxins, which cause hematomas, haemorrhages and petechias (39, 46).

Systemic symptoms may accompany local symptoms. Nausea, dizziness, tachycardia, vomiting, abdominal cramps, diarrhoea and weakness are almost always present (39) (46). The cardiovascular system of the patient is generally affected, causing dangerous medical conditions, such as hypotension and arrhythmias and occasionally high blood pressure levels as well. Regional lymphadenopathy can also occur. Mostly the venom of the individuals populating the South-western region of the country can affect the peripheral nervous system, primarily the cranial nerves, thus often inducing diplopia, ptosis, dysarthria and/or impaired vision (39, 46).

2.10 Pathophysiology underlying venom-induced neurotoxicity

Reports of neurological manifestations in patients bitten by *V. b. bosniensis* have been published in the last couple of years (Persson, 2015) thereby expanding the knowledge on the clinical presentation of envenomings. Earlier (47, 48), already emphasized that the venom of the Serbian adders living in the Sava Valley can induce peripheral neurotoxicity in humans. These lowland adder populations are currently also recognized as *V. b. bosniensis* (49). Oculomotor nerve palsy, as a characteristic sign in patients bitten by specimens of adder

populations in Somogy County, was initially mentioned by Fejérváry (50) without a detailed description, though.

The pathopysiological explanation for peripheral neuromuscular weakness after snakebite is caused by the venom's effect to disrupt the neuromuscular junction transmission (51). Neurotoxins produce their effect at the site of the neuromuscular junctions pre- or post-synaptically. As a response to the incoming nerve action potential causing the influx of calcium ions the motor nerve axon terminal synthesises and releases the neurotransmitter acetylcholine (ACh) (52-54). This process is the result of an intracellular signalling cascade involving SNARE proteins (52-54). Nicotinic acetylcholine receptors (nAChRs) enable the release of ACh. Disturbances of neuromuscular transmission can occur at the presynaptic level, affecting calcium and potassium channels, SNARE proteins or nAChRs (51).

As Ach is released into the synaptic cleft, it is degraded by acetyl cholinesterase, in order to terminate its action.

Post-synaptically, ACh binds to muscle nAChRs, which are ligand-gated ion channels. End-plate potential is effected through the influx of sodium and calcium ions and efflux of potassium (52-54). If adequate Ach is released, muscle contraction occurs. Post-synaptical neuromuscular block can be depolarising or non-depolarising. Depolarising neuromuscular blocking agents, such as suxamethonium bind irreversibly to the post-synaptic muscle nAChRs, while non-depolarising blocking agents such as curare competitively inhibit Ach binding to nAchRs (52-54). It follows that these latter neuromuscular blocking agents can be antagonized by acetyl choline esterase inhibitors (AChEis), like neostigmine. It has also been shown that non-depolarising agents can produce pre-synaptic effects as well, which is neurophysiologically demonstrated by the combination of reduction in twitch amplitude (indicating post-synaptic blockade) and fade of the twitch height responses on repetitive stimulation (due to pre-synaptic) blockade (52-54).

Snake neurotoxins can have pre- or post-synaptic activity. Pre-synaptic snake toxins have potent phospholipase A2 (PLA2) activity, while post-synaptic snake toxins include alpha-bungarotoxin and candoxin to name a few (51).

Figure 3 shows the sites of action of snake neurotoxins and other substances on the neuromuscular junction. (51)
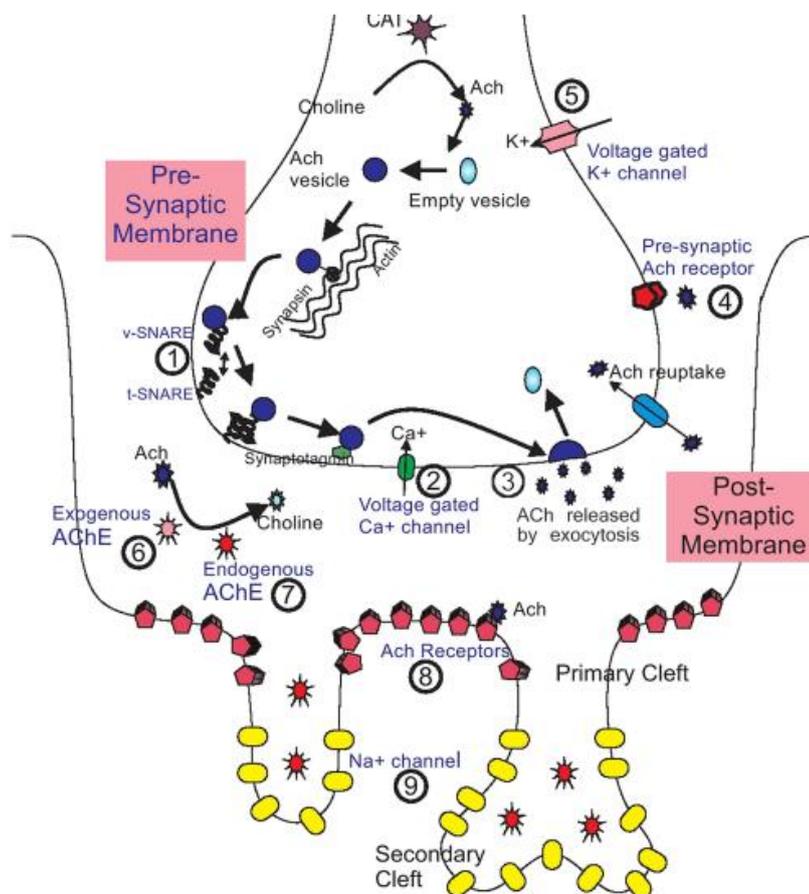
Sites of action of snake neurotoxins and other substances on the neuromuscular junction.
Schematic representation of the neuromuscular junction showing different sites of action of snake neurotoxins, other toxins, and pharmacological substances, and sites of involvement in disease states (examples indicated where relevant).
1. Synaptic vesicular proteins: _Snake toxins:_ beta-bungarotoxin (*Bungarus spp.*), taipoxin (*O. scutellatus*); _Other toxins:_ botulinum toxin, tetanus neurotoxin.
2. Voltage-gated calcium channel: _Snake toxins:_ calciseptine (*Dendroaspis spp.*), beta- bungaratoxin (*Bungarus spp.*); _Other toxins:_ omega-conotoxin (marine snail, *Conus spp.*); Disease states: Lambert-Eaton myaesthenic syndrome.
3. Pre-synaptic membrane: _Snake toxins:_ phospholipase A2 toxins.
4. Pre-synaptic ACh receptor: _Snake toxins:_ candoxin (*Bungarus candidus*); _Other toxins:_ curare; _Pharmacological substances:_ non-depolarising blocking drugs (atracurium).
5. Voltage-gated potassium channels: _Snake toxins:_ dendrotoxins (*Dendroaspis spp.*); _Disease states:_ neuromyotonia, Isaacs' syndrome; _Pharmacological substances:_ magnesium sulphate, aminoglycosides.
6. Acetylcholine: Lysis by exogenous acetylcholinesterase in _snake venom:_ cobra venom (*Naja spp.*).
7. Acetylcholinesterase: Inhibitors of endogenous AChE in _snake venom:_ fasiculins (*Dendroaspis spp.*).
8. Post-synaptic ACh receptors: _Snake toxins:_ alpha-bungaratoxin (*Bungarus spp.*), candoxin (*B. candidus*), azemiopsin (*A. feae*), waglerin (*T. wagleri*); _Other toxins_: alpha-conotoxin (marine snail, *Conus spp.*); _Disease states:_ myasthenia gravis; _Pharmacological substances:_ depolarising blocking agents (e.g., succinylcholine), non-depolarising blocking drugs (e.g., atracurium).
9. Voltage-gated sodium channels: _Snake toxins:_ crotamine (*Crotalus spp.*); _Other toxins:_ pompilidotoxin (wasps), delta-conotoxin (*Conus* spp.), tetradotoxin (pufferfish).

Figure 3: Sites of action of snake neurotoxins and other substances on the neuromuscular junction

Adapted from Neurotoxicity in snakebite--the limits of our knowledge. by Ranawaka UK et al. Negl Trop Dis. 2013 Oct 10;7(10):e2302

2.11 The aims of the case report on V. b. bosniensis envenomation

The aim of this publication is to expand the knowledge about the envenoming due to *V. b. bosniensis* bite by describing a case which resulted in minimal local symptoms but severe neurological manifestations and other, persistent systemic venom effects in an adult patient. This is the first photographically-documented neurotoxic case that occurred in South-Western Hungary, in the northernmost geographical distribution range of this taxon.

2.12 The goals of my study

Taken together, the <u>goals of my studies</u> were to determine the following:

Regarding the study on ECG alterations in normokalemic vs hyperkalaemic patients:

1. Are there any differences between the baseline characteristics (age, comorbidities, medication, mortality rate) of normokalemic and hyperkalemic patients admitted to the Emergency Department?

2. What is the frequency of ECG alterations suggestive of hyperkalemia in patients with normokalemia, moderate hyperkalemia and severe hyperkalemia?

3. What kind of ECG alterations indicative of hyperkalemia were more common in patients with moderate or severe hyperkalemia than in patients with normokalemia?

4. Are there any differences between the frequency of ECG alterations possibly associated with hyperkalemia, such as atrial fibrillation, short or long QTc and ST depression, in normokalemic versus hyperkalemic patients?

5. Is there a correlation between the occurance of certain ECG alterations and the severity of hyperkalemia?

6. Is the ECG a suitable tool in the diagnosis of hyperkalemia in the prehospital, emergency setting?

   Should therapeutic decisions and interventions be made based on the ECG signs of hyperkalemia alone?

Regarding the case report on V.b. bosniensis envenoming:

7. Which characteristic and non-characteristic symptoms of the the European *Vipera* spp. envenomings were present in our case report of a patient following a *Vipera berus bosniensis* bite, which occured in South-Western Hungary?

8. Which unique clinical signs of snakebite neurotoxicity could be observed in our patient following *Vipera berus bosniensis* envenoming?

9. Do the neurotoxic components of Vipera berus bosniensis cause a disturbance in the neuromuscular junctions?
    If so, how can this disturbance be objectively observed?

10. What is the possible explanation for the slowly evolving and prolonged neurological manifestations observed in our patient following the snakebite?

11. What are the clinical implications of our case report in the treatment of snakebites at the Emergency Department?

3   Materials and Methods

Regarding the study on ECG alterations in normokalemic and hyperkalemic patients

3.1   Study design

This was an observational retrospective study performed at the Emergency Center of the Kaposi Mór General Hospital in 2013. The study received ethical approval from the regional ethical committee, the Institutional Ethics and Research Ethics Committee of the Somogy County Kaposi Mór Teaching Hospital prior to the research procedure (Reference number: IG/02401-002/2015)

3.2   Patients

The annual census of the Emergency Center is approximately 35 000 patients and 80% of the patients are over 18 years of age. The medical records of adult patients admitted to the Emergency Center between 01.01.2013.-31.12.2013 were chosen randomly from the database of the Emergency Department. We selected 180 patients with normokalemia (3.4-5.1mmol/l) and 182 patients with moderately (6.0-7.0 mmol/L) or severely (>7.0 mmol/L) elevated serum or plasma potassium levels, randomly. All patients chosen for our study were adults, over 18 years of age. Patients were required to have had an ECG performed within one hour of the laboratory draw. The drawing of the blood and the storage and transport of the blood samples adhered to the regulations of the Emergency Center in order to prevent obtaining false test results. Laboratory analysis of the blood samples was intiatated within 30 minutes of the blood draw. Patients with hemolysed samples were not included in the study. From the hyperkalemic group, patients with preanalytical errors (15 patients) and patients whose ECG recordings could not be completely analyzed due to technical reasons (16 patients) were excluded as well as patients with multiple presentations (16 cases) within the given interval. Only the first presentation to the Emergency Center was included. In the group with normokalemic patients, 10 patients were excluded due to missing ECG or missing potassium values. Finally, electrocardiograms and data from 135 hyperkalemic (moderate hyperkalemia n=97, severe hyperkalemia n=38) and 170 normokalemic patients were analyzed.

3.3 Laboratory tests

Potassium levels were measured in the Central Laboratory of the Moritz Kaposi General Hospital with Cobas 8000-C702 module according to the protocol of the manufacturer (Roche Diagnostics International AG, Switzerland). The normal range of the potassium level was 3.4-5.1 mmol/l. Point-of-care measurement of potassium was not available, and therefore not used in our study.

3.4 Study protocol

Data including the medical history, comorbidities and medication record were abstracted from the electronical medical record of the hospital. The following data were gathered from each record: demographics (age, gender), serum and plasma potassium levels, ECG, laboratory values (creatinine) obtained on same draw as the potassium level, comorbidities of the patients at the date of admission, medication taken by patients prior to obtaining the ECG, occurance of cardiac arrest. Data was independently reviewed by two investigators.

3.5 ECG analysis

The ECG curves of each patient – recorded within one hour of the blood draw - were analyzed by two board-certified emergency physicians, independently. Since multiple ECG instruments were used, ECG-machine based ECG interpretations were not included in the study. The resulting varied ECG interpretations would have led to inaccuracy in the evaluation of the ECGs. The physicians were blinded to the objectives and method of the study, to all of the laboratory values (including potassium values), the particular clinical diagnoses and medical histories as well as to each other's readings. Neither reader was a caregiver for any of the study subjects. Each ECG was examined for the following: rhythm, heart rate, PR interval, AV block, length of QRS interval, ST-T alterations, length of QTc interval. Cardiac arrest was documented in cases of pulseless electrical activity, pulseless ventricular tachycardia, ventricular fibrillation or asystole. PR interval was considered "prolonged" if PR duration> 200ms, QRS interval was considered "wide" if the QRS duration was > 110ms. QTc interval was deemed short if QTc<350ms and prolonged, if QTc> 450ms. The intervals used in our study were based on previous literature on ECG analyses (55) T waves were considered peaked if they were symmetrical and had a large amplitude based on the investigating physician's judgement, ECG alterations were considered suggestive of

hyperkalemia if the following were recorded: AV junctional escape rhythm, Ventricular escape rhythm, bradycardia, Ist-IInd-IIIrd degree AV blocks, wide QRS, peaked T-waves. Although not generally considered typical ECG manifestations of hyperkalemia, the following ECG changes were also recorded: atrial fibrillation, ST depression, short QTc and prolonged QTc.

3.6 Statistics

Data was analysed using SPSS22 software. In order to test for association of each parameter with measured potassium values, χ^2 test, or Fischer exact tests were used as appropriate. P values ≤ 0.05 were considered to be statistically significant.

4 Results

Related to the study: ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients

4.1 Patient characteristics

Data was collected from 135 hyperkalemic (potassium > 6.0 mmol/l) and 170 normokalemic (potassium 3.4-5.9 mmol/l) patients. Gender distribution between the two groups was similar. Patients in the hyperkalemic group were older than patients in the normokalemic (control) group. Almost a third (29.6%) of the hyperkalemic patients suffered from chronic kidney disease (CKD), while only 8.8% of the normokalemic patients had CKD. Accordingly, preceding renal replacement therapy among hyperkalemic patients was significantly more frequent than among normokalemic patients. Regarding medication, a significantly higher percentage of hyperkalemic patients took angiotensin receptor blockers, angiotensin coverting enzyme inhibitors, non steroid analgesics, potassium supplements, and diuretics such as amilorid and spironolactone and other diuretics, like furosemide and thiazides (data not shown) than normokalemic patients. Comorbidities, such as heart failure, diabetes mellitus, liver failure, sepsis, cancer and dehydration were also significantly more prevalent in hyperkalemic patients. There was no significant difference between the prevalence of hypertension between normo- and hyperkalemic patients. Mortality within 72 hours of admission was high (13.3%) in the hyperkalemic group compared to only 2.4% of normokalemic patients. Data regarding patient characteristics are shown in *Table 3*.

	Control (n=170)		Hyperkalemia (n=135)	
Age (years)	**60.45± 15.95**		**70.61± 13.93**	
	%	**n**	**%**	**n**
Female	54,7%	93	51,9%	70
Prior CKD	8,8%	15	29,6%*	40
Prior RRT	1,2%	2	7,4%*	10
Exit in 72h	2,4%	4	13,3%*	18
need of RRT	0,0%	0	15,6%*	21
HF	11,8%	20	32,6%*	44
DM	20,6%	35	36,3%*	49
HT	64,1%	109	73,3%	99
Liver failure	4,1%	7	11,1%*	15
Sepsis	1,2%	2	14,8%*	20
Neoplasia	14,1%	24	29,6%*	40
Dehydration	10,0%	17	31,1%*	42
B-blocker	38,8%	66	45,9%*	62
Digitalis	4,1%	7	5,9%	8
ACEi	37,6%	64	54,8%*	74
ARB	10,6%	18	14,1%*	19
Spironolactone	4,7%	8	15,6%*	21
Amilorid	1,2%	2	14,1%*	19
NSAID	8,2%	14	16,3%*	22
K suppl	15,3%	26	35,6%*	48

*Table 3: Baseline characteristics of normokalemic (control) and hyperkalemic patients. (CKD: chronic kidney disease, RRT renal replacement therapy, HF: heart failure, DM: diabetes mellitus, HT: hypertension, K suppl: potassium supplementation, * : p≤0,05)*

4.2 The frequency of ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients

The frequencies of ECG alterations suggestive of hyperkalemia were recorded in patients with normokalemia, moderate hyperkalemia and severe hyperkalemia.

In the control group, 24.0% of normokalemic patients had ECG alterations suggestive of hyperkalemia and from these, 20% had one and 4% had 2 or more ECG changes indicative of hyperkalemia. Less than half of the patients (46%) with moderate or severe hyperkalemia had some form of ECG manifestation suggestive of hyperkalemia. 29% of severely hyperkalemic patients had no ECG changes indicative of hyperkalemia. From the 46% of hyperkalemic patients exhibiting some form of hyperkalemic ECG manifestation, 30% had one and 16% had two or more ECG alterations suggesting hyperkalemia. *(Table 4, Figure 4)*

		1 ECG alteration	≥2 ECG alterations	Cardiac arrest	AV junctional escape	Ventricular escape	Bradycardia	I°degree AV-block	II°degree AV-block	III°degree AV-block	Wide QRS	Peaked T-waves
Control (n=170)	%	20%	4%	0.0%	0.0%	0.0%	6.5%	7.1%	0.0%	0.0%	8.2%	4.7%
	n	34	7	0	0	0	11	12	0	0	14	8
All hyperkalemia (n=135)	%	30%	16%	5.9%	5.2%	0.7%	12.6%	8.1%	0.0%	0.7%	18.5%*	9.6%
	n	41	21	8	7	1	17	11	0	1	25	13
Moderate hyperkalemia (n=97)	%	27%	9%	3.1%	5.2%	1.0%	10.3%	4.1%	0.0%	0.0%	13.4%	6.2%
	n	26	9	3	5	1	10	4	0	0	13	6
Severe hyperkalemia (n=38)	%	39%	32%	13.2%	5.3%	0.0%	18.4%*	18.4%*	0.0%	2.6%	31.6%*	18.4%*
	n	15	12	5	2	0	7	7	0	1	12	7

Table 4: Frequency of ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic (moderate and/or severe) patients (: p≤0,05), Cardiac arrest included asytole, ventricular fibrillation, pulseless ventricular tachycardia and pulseless electric activity.*
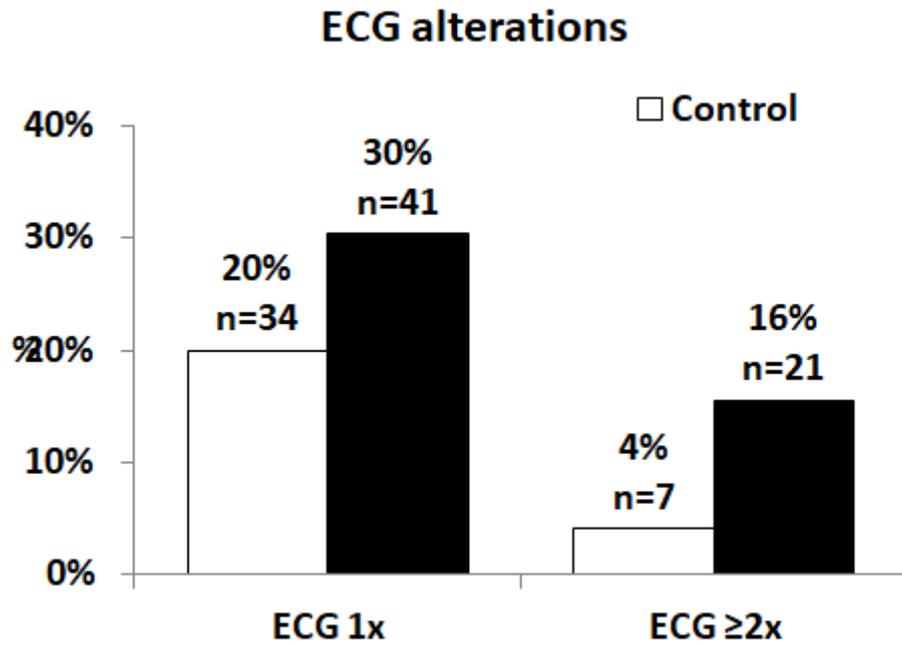
ECG alterations

Figure 4: The frequency of single and multiple ECG alterations suggestive of hyperkalemia in normokalemic and hyperkalemic patients

Significantly more patients with severe hyperkalemia had wide QRS (31.6%), bradycardia (18.4%), peaked T-waves (18.4%) and 1st degree AV block (18.4%) compared to normokalemic patients (8.2%, 6.5%, 4.7%, and 7.1%, respectively). Wide QRS (31.6%) was the most common ECG alteration in severely hyperkalemic patients and in the normokalemic group as well.*(Table 4, Figure 5.)*There was no significant difference in the frequency of ECG alterations suggestive of hyperkalemia between the normokalemic and the moderately hyperkalemic groups. *(Table 4, Figure 5)*
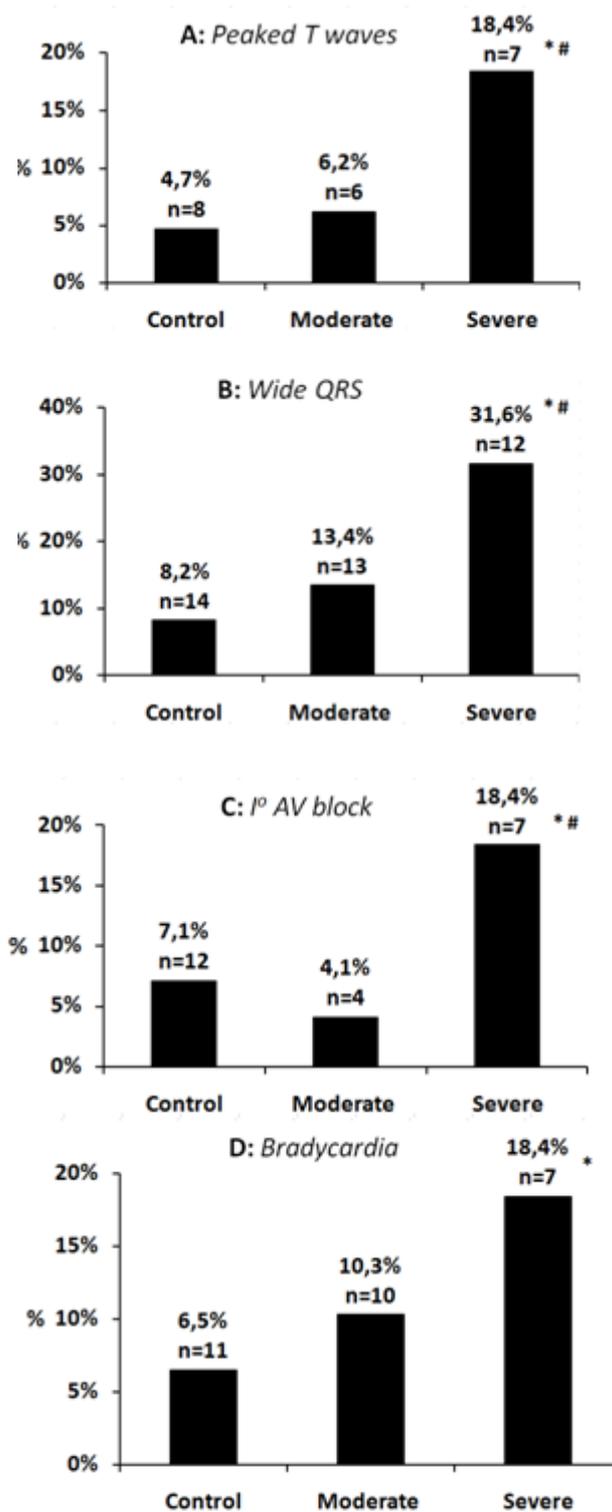
Figure 5: The frequency of ECG alterations suggestive of hyperkalemia in normokalemic, moderately hyperkalemic and severely hyperkalemic patients (: p<0.05 vs control, #: p<0.05 vs moderate hyperkalemia) A: Peaked T waves; B: Wide QRS; C: Ist degree AV block; D: Bradycardia*

When normokalemic patients were compared to all (moderately + severely) hyperkalemic patients, we found that wide QRS (18.5%) was the only ECG alteration significantly more frequent in all hyperkalemic patients compared to normokalemic patients (8.2%). AV junctional rhythm was seen only on the ECG of hyperkalemic (moderate or severe) patients but was not present on ECG recorded for normokalemic patients. *(Table 4, Figure 5)*

Cardiac arrest occurred in 8 patients with hyperkalemia and 5 of these patients had severely high potassium levels. None of the patients with normal potassium levels had cardiac arrest. *(Table 4)*

4.3 The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients

Frequency of ECG abnormalities possibly associated with hyperkalemia including atrial fibrillation, QTc changes and ST depression were registered.

There was no significant difference regarding the frequency of ST depression between patients with normal or increased levels of potassium. Atrial fibrillation was significantly more frequent in severely hyperkalemic patients (26.3%) compared to normokalemic patients (10.6%). However, no significant difference regarding atrial fibrillation was detected between the moderately hyperkalemic and the normokalemic groups. Prolonged QTc was the only ECG alteration which was significantly more prevalent in both patients with moderate (17.5%) and severe hyperkalemia (21.1%) compared to patients with normokalemia (5.3%). *(Table 5, Figure 5).*

		AF	ST depression	Short QTc	Prolonged QTc
Control (n=170)	%	10.6%	28.8%	0.0%	5.3%
	n	18	49	0	9
All hyperkalemia (n=135)	%	15.6%	23.0%	0.7%	18.5%*
	n	21	31	1	25
Moderate hyperkalemia (n=97)	%	11.3%	22.7%	1.0%	17.5%*
	n	11	22	1	17
Severe hyperkalemia (n=38)	%	26.3%*	23.7%	0.0%	21.1%*
	n	10	9	0	8

Table 5: The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients. (: p≤0.05)*

4.4 The association between the occurance of certain ECG alterations and the severity of hyperkalemia

We investigated whether the elevations of potassium levels increased the occurrence of certain ECG alterations. The following differences were found between moderately and severely hyperkalemic patients: atrial fibrillation (11.3 vs 26.3%, χ^2 test, p<0.05), I^o AV block (4.1% vs 18.4%, Fisher exact test, p<0.05,) wide QRS (13.4% vs 31.6%, χ^2 test, p<0.05) and peaked T waves (6.2% vs 18.4%, Fisher exact test, p=0.05) were present more frequently on the ECG recordings of patients with severe hyperkalemia than on the ECG of patients with moderate hyperkalemia. *(Figure 5, Figure 6)*
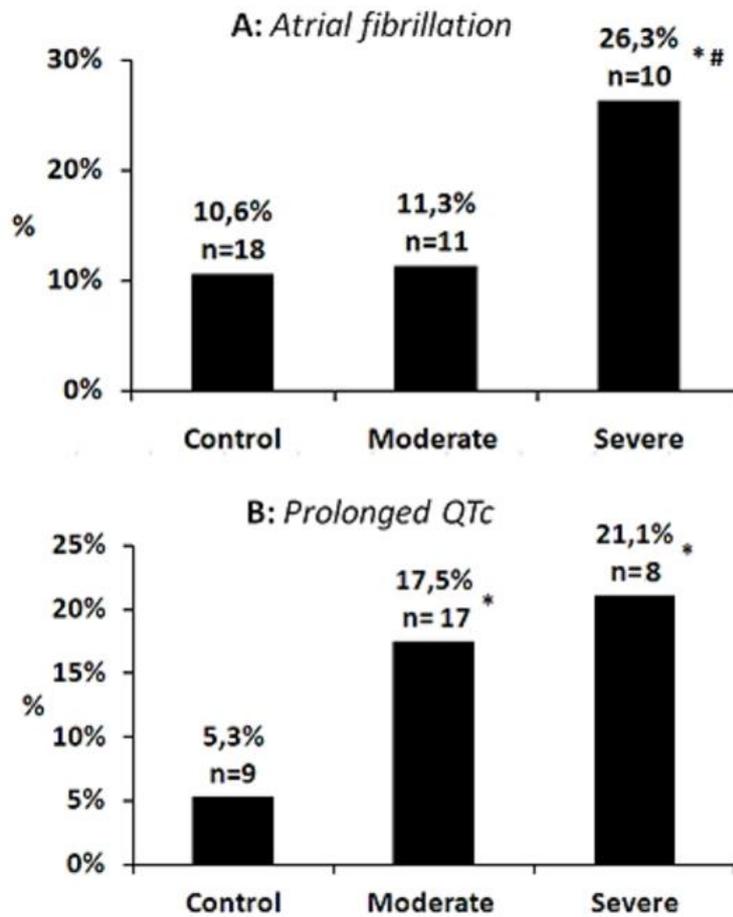
Figure 6: The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients

4.5   Report of a patient following *V. b. bosniensis* envenomation

Case report

A 63-year-old man was bitten by an adder in Kaszó, Somogy County, South-Western Hungary on **May 04th, 2017** between 13:30 and 13:45. Medical history of the patient included sinus bradycardia (heart rate: 45/min) diagnosed in 2015 and hypertension. The latter condition was controlled by Tolura® (telmisartan, 80 mg daily). He had had a normal coronary angiogram in 2014. He had no known allergies and had not suffered any snakebites previously. He took his telmisartan tablet on the morning of the accident. The patient indicated he did not consume alcohol preceding the incident or on a regular basis.

The patient found a uniformly black snake in his garden which he wanted to show his wife before removing it. The snake bit the patient's left index finger when he grabbed it. A burning pain developed immediately at the site of the bite. Although the patient knew that he was bitten by a viper – because of the burning pain emerging immediately – he was not certain about the exact species and did not want to risk another bite, therefore he preserved the specimen for exact identification and took a photograph of it. The animal was later identified by an expert as a sub-adult, melanistic specimen of *V. b. bosniensis* (length was about 38-40 cm) based on the native distribution area of the taxon and the photograph taken (*Figure 2 C*). The patient immediately started to squeeze the blood out of the bite site. He experienced sweating and nausea combined with stomach ache in the first 10 minutes following the snakebite. His wife transported him by car to the nearest hospital in Nagyatád. He vomited three times during the transport.

Upon arrival **(at 14:10)** at the hospital in Nagyatád two fang marks were clearly identifiable on the proximal nail fold of the left index finger. A small local haematoma and minimal local swelling were visible around the fang marks. The patient complained of nausea and dizziness and vomited once more. He also complained of abdominal pain during the medical examination. A blood pressure reading of 120/80 mmHg was recorded with mild tachycardia (90/min). An ECG was performed at 14:21, showing horizontal ST depression in leads V5-6 (*Figure 7*).
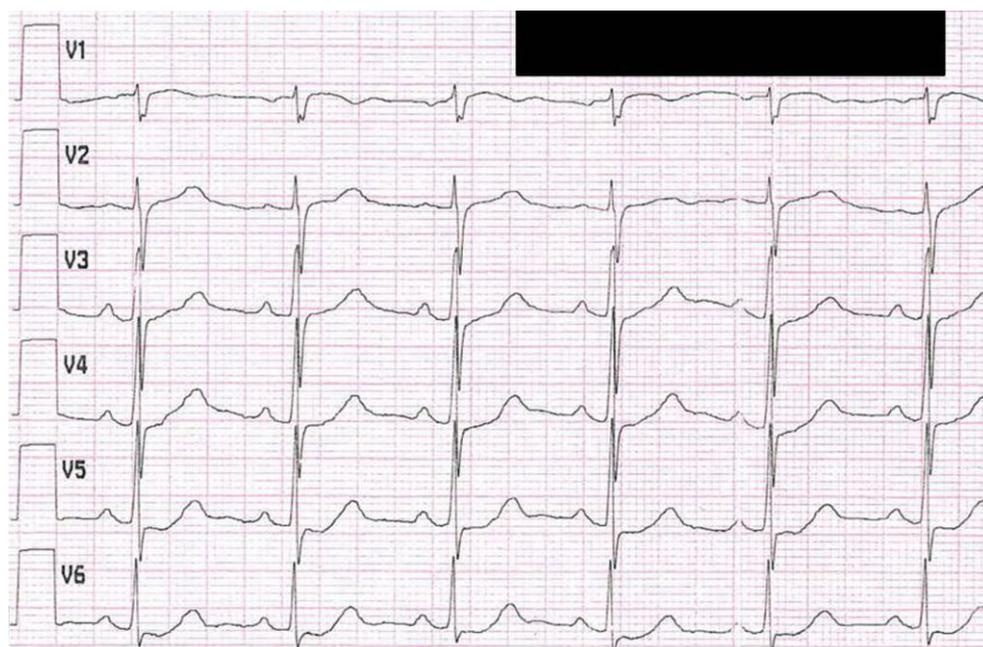

Figure 7: ECG changes of patient showed transient horizontal ST depression in V5-6.
The patient's date of birth and name are blinded by black rectangle.

Isolyte infusion (500 ml) and antiemetic medication (metoclopramide, 10 mg i.v.) were given. The patient was transferred by ambulance to the Emergency Department of Somogy County "Moritz Kaposi" General Hospital in Kaposvár. The abdominal muscles were very tender, and guarding was detected upon palpation on the way to the hospital. He vomited again in the ambulance. The following blood pressure, heart rate and oxygen saturation levels were recorded during the transportation: 160/100 mmHg, 77/min, 98% (14:35); 166/105 mmHg, 71/min, 98% (14:40); 165/105 mmHg, 69/min, 98% (14:50); 160/100 mmHg, 69/min, 98% (15:00).

Upon admission **(at 15:05)** at the Emergency Center of Somogy County "Moritz Kaposi" General Hospital in Kaposvár the patient was pale, weak and sweating. He still complained of nausea. His consciousness remained normal and the patient was able to answer questions adequately. The last digit of the bitten finger was swollen. The following vital parameters were recorded: blood pressure: 140/70 mmHg; heart rate: 74 /min; SO2: 98 %, body temperature 36.5°C. The initial routine laboratory findings included: serum potassium 3.39 mmol/l (normal range: 3.70-5.40); absolute neutrophil count 8.52 g/l (normal range: 2.00-8.50), and blood glucose 9.4 mmol/l (normal range: 3.3-5.5). In the first 30 minutes of observation the patient vomited twice. Tenderness of the abdominal muscles was replaced by intense abdominal colic and the patient developed profuse diarrhoea (produced high volume, loose stools on two occasions). The patient was admitted to the Intensive Care Unit of the Emergency Department. The hypersensitivity skin test (at 15:28) yielded negative results; antivenom therapy (500 IU i.m. Viper Venom Antitoxin®, Biomed, Warsaw (monovalent antivenom, *V. berus* venom is used in its production)) was applied at 15:48. As supportive care the patient received chloropyramine (20 mg i.v.), and methylprednisolone (125 mg i.v.). Debridement (cleansing with aqueous solution of 10% povidone-iodine and hydrogen peroxide solution) and anaesthesia (nerve block by Oberst's method) were performed locally followed by removal of the superficial tissues around the fang marks on the bitten finger *(Figure 8)*.

Figure 8: Local swelling of the bitten finger with mild, small haematoma. Tissue was surgically removed around the puncture mark. (Photograph taken by Dr Csaba Varga.)

The next morning **(05 May, at 08:20)** the patient was unable to open his eyes. When raising the upper eyelids manually, he reported constant double vision. He reported that the images seen before him were displaced horizontally. He was unable to move his eyes upward. The pupils were equal in size and moderately dilated, the pupillary light reflexes were intact. Complete bilateral ptosis with external ophthalmoplegia was diagnosed on neurological examination (*Figure 9*).
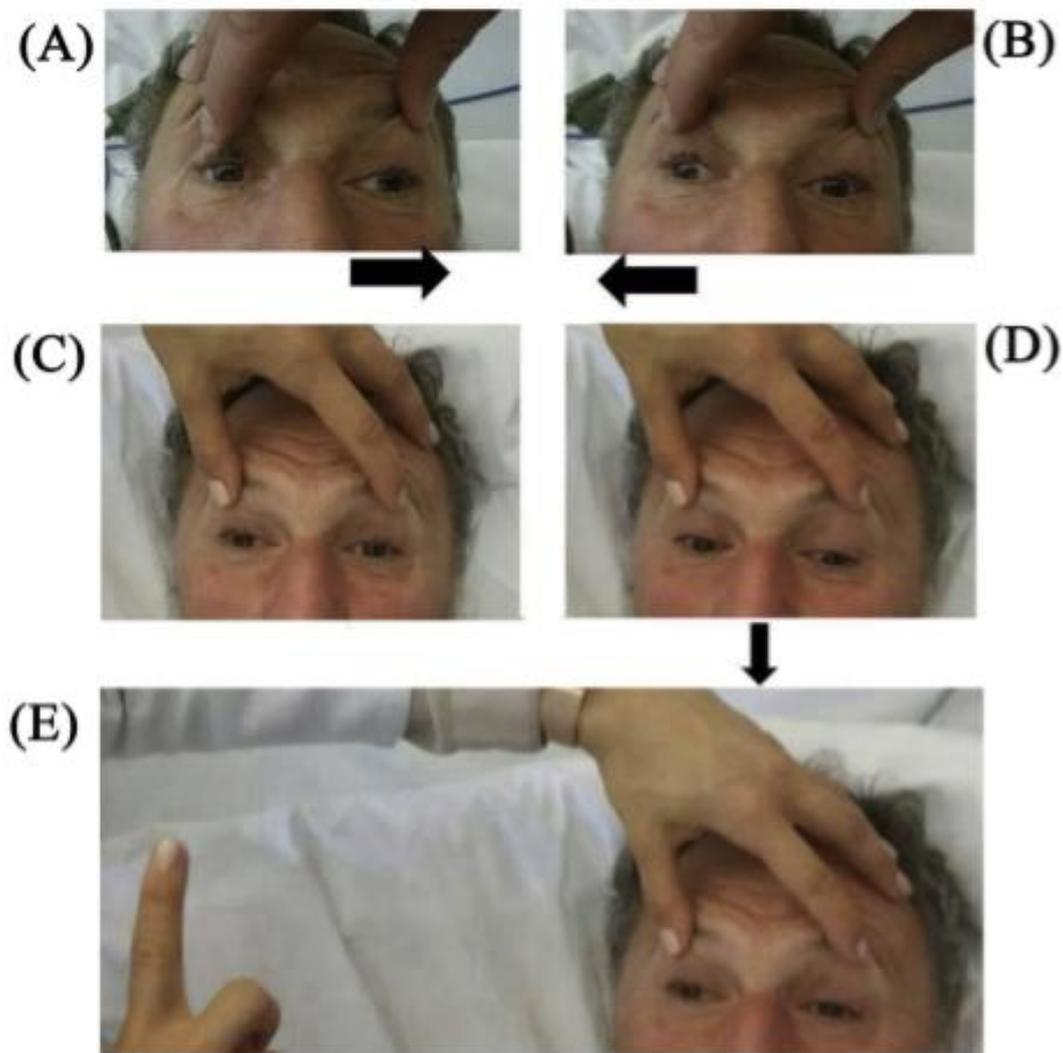
Figure 9: Complete bilateral ptosis and ataxic nystagmus in the patient. (A): Gaze to right, abducted right eye shows paralysis of left medial rectus.(B): Gaze to left, abducted left eye shows paralysis of right medial rectus. (C) and (D): The eyeballs diverged both horizontally and vertically while looking ahead. (E): The left eye did not cross the midline when the patient attempted to look to the right, whereas the right eye did not cross the midline when he attempted to look to the left. (Photographs were taken by Dr Gergely Bilics. The patient verbally contributed to taking and publishing of photos.)

The eyeballs diverged both horizontally and vertically while looking ahead. The left eye did not cross the midline when the patient attempted to look to the right, whereas the right eye did not cross the midline when he attempted to look to the left. At 10:30, single-fiber electromyography (SfEMG) was performed following neurological consultation. The SfEMG record is shown in *Figure 10*.
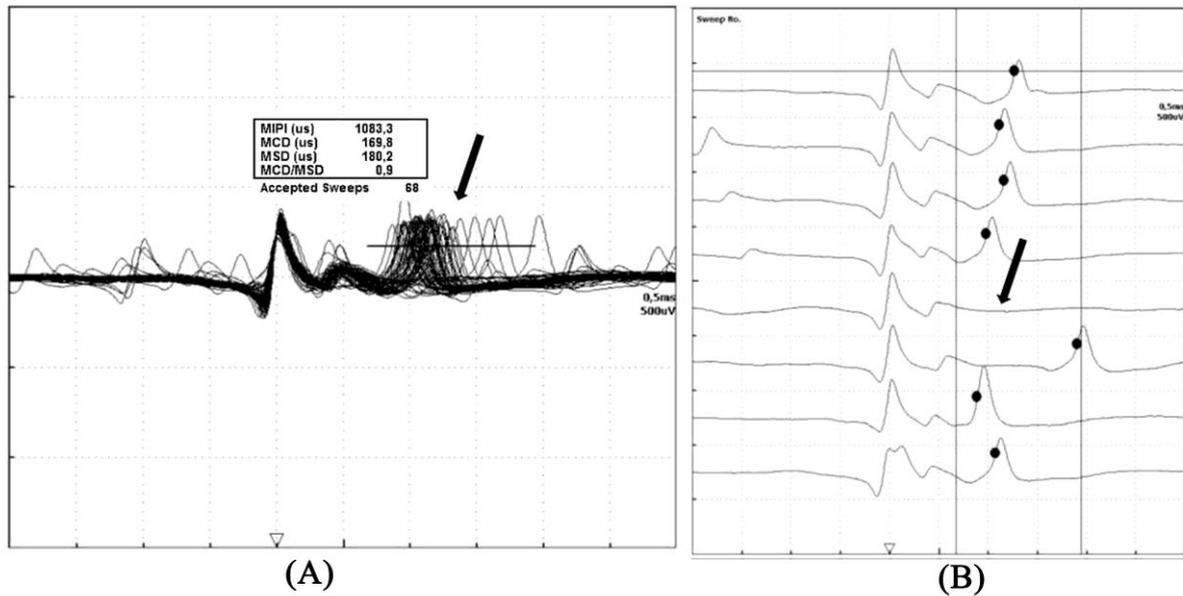
Figure 10: A pair of action potentials recorded from the envenomed patient during voluntary activation of the right orbicularis oris muscle. The oscilloscope is triggered by the rising portion of the first potential, which falls at the same position with each discharge. Legend: (A): Consecutive discharges are superimposed. (B): The second potential falls at varying positions (black dots) among successive discharges, demonstrating the neuromuscular jitter. The sweep is triggered on the first potential, and increased jitter is seen in the second potential. Gain: 500mV/div, sweep time: 0.5 ms/div

By 12:56 the localised swelling on the bitten finger was not apparent any more. At 16:00, the patient received neostigmine-methylsulfate (0.5 mg i.v.) in infusion and an atropine-sulfate (0.5 mg i.m.) injection. The laboratory findings are listed in *Table 6*.

Laboratory findings	Reference range	Unit	04 May	05 May	06 May	07 May	08 May 05:41
blood glucose [a]	3.3-5.5	mmol/L	**9.4**	**8.3**	‡	4.6	4.6
C-reactive protein [b]	0.0-5.0	mg/L	‡	**14.9**	‡	4.5	‡
glutamic-pyruvic transaminase [c]	0-50	U/L	18	16	‡	17	**91**
Absolute neutrophil count [d]	2.0-8.50	G/L	**8.52**	‡	‡	‡	4.68
Red blood cell [e]	4.50-5.90	G/L	5.24	4.64	‡	**4.46**	4.78
Haemoglobin [f]	140-175	g/L	157	**138**	‡	**103**	143
Serum potassium [g]	3.70-5.40	mmol/L	**3.39**	4.13	‡	3.90	4.15

Deviations are bold. ‡= not measured.

[a]= Elevated blood glucose level is described in moderate and high-grade viper envenomings in Europe (Westerström et al., 2010; Garkowski et al., 2012; Stoyanova et al., 2012; Malina et al., 2013; Claudet et al., 2016).
[b]= Value of C-reactive protein can also increase in *V. berus* envenomings (Magdalan et al., 2010; Garkowski et al., 2012).
[c]= Elevated level of transaminase can occur in envenomed patients by *V. berus* (Warrell, 2005a; Magdalan et al., 2010; Garkowski et al., 2012).
[d]= Neutrophil leucocytes is frequently diagnosed in *V. berus* bites (Warrell, 2005a; Magdalan et al., 2010; Garkowski et al., 2012) but it was almost normal in our patient.
[e]= Reducing tendency of red blood cells can be detected in envenomed patients by *V. berus* (Warrel, 2005a; Hoegberg et al., 2009).
[f]= Haemoglobin level may initially increase and then, reduces during the envenoming, associating with anaemia (Karlson-Stiber et al., 2006; Hønge et al., 2015).
[g]=Different degree electrolyte imbalance may also occur following the bites by *Vipera* spp. (Persson, 2015).

Table 6: Detected changes in the patient's laboratory values during the course of envenoming

On **06 May**, the patient felt weak and still had ptosis but he was already able to open his eyelids to uncover the pupils. He complained of severe double vision, intense dizziness, and felt "drunk". Although he was able to walk obvious signs of imbalance and unsteady gait were apparent. The vital parameters remained stable. By the end of **07 May**, the ptosis resolved, ophthalmoplegia started to resolve but the patient was still experiencing double vision. No new medical event occurred during the night.

On **08 May (at 09:20)**, the ptosis resolved as well as the paralysis of the extraocular muscles. He reported double vision only on sudden lateral gaze (at this stage the image seen was "delayed"). The patient was discharged from hospital with stable vital parameters at 14:00. The medicinal therapy recommended for home included benfotiamin (300 mg daily). The patient's diplopia - as the last symptom of the envenoming - resolved completely on **13 May** based on the follow-up information obtained from the patient by the physician treating the patient.

5   Discussion

5.1   Discussion related to the study on: "ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients"

Hyperkalemia is one of the most common, potentially life-threatening metabolic disorders of reversible periarrest conditions that needs to be recognized and treated in time (56). Potassium levels above the normal range often remain unnoticed and periarrest situations may occur without warning (57). The recognition of patients with hyperkalemia poses challenges and there are often delays in the initiation of the electrolyte disorder's treatment. According to a study conducted in an Emergency Department in the U.S., the mean time from triage to treatment of patients with potassium levels 6 mmol/l or above, was 117 minutes. (26). Furthermore, a mean 1-hour- long delay between the time of laboratory notification of hyperkalemia and initiation of treatment was found, despite recommendations for "immediate therapy" for serum potassium levels over 6 mmol/l (26, 58). Based on a review of the medical charts, underlying reasons for the delay were found to be: diagnostic uncertainty (in many cases the physician's reaction to an unexpectedly high potassium level was to repeat the blood test and to acquire an ECG) or the difficulties in obtaining intravenous access (26).

Electrocardiography is a widely used, easily attainable method to raise the possibility of hyperkalemia, however there have been conflicting reports about its sensitivity and specificity to signal elevated potassium levels (16, 26, 59). An earlier report by Wrenn et al. investigated whether physicians blinded to the serum potassium level could predict hyperkalemia from the ECG (59). The report showed that the ECG readers' ability to predict the severity of hyperkalemia was poor (59). The sensitivities of the readers for predicting hyperkalemia were .43 and .34 and the specificities for detecting hyperkalemia were .85 and .86. (59). The study concluded that even in high-risk patients, the ECG was not a sensitive method of detecting hyperkalemia (59). A subsequent retrospective review of the frequency of ECG changes in hyperkalemia also found that the electrodiagram was insensitive for diagnosing hyperkalemia, although the probability of ECG changes increased with the elevation of serum potassium levels (25). Other reports stated that there was a predictable progression of ECG alterations with the elevation of serum potassium levels (16). The most recently conducted study by Rafique at al. in which 528 ECGs from ESRD patients were evaluated found that the ECG

was not a sensitive method of detecting hyperkalemia, but that its high specificity for detecting high potassium levels could be used as a rule in test. (60)

In our study we investigated whether ECG alterations suggestive of hyperkalemia were present in a randomly selected group of normokalemic patients admitted to the Emergency Center. ECGs have often been shown to be normal in hyperkalemia and a number of cases have been reported where patients with severely elevated potassium levels did not show typical ECG manifestations (27, 59). In accordance with these investigations, we found that less than half of the hyperkalemic patients exhibited ECG changes suggestive of hyperkalemia, while the majority of the hyperkalemic patients showed no typical ECG changes at all. A surprisingly high proportion (24%) of normokalemic patients exhibited ECG alterations suggestive of hyperkalemia. Thus, based on ECG analysis alone, normokalemia and hyperkalemia cannot be confirmed or exluded in patients.

A study conducted in the United States on hemodialysis patients with hyperkalemia investigated the prevalence of ECG changes in stable patients with ESRD (19). According to this study, none of the patients had arrhythmia or any of the typical electrocardiographic alterations suggestive of hyperkalemia and no significant difference was found in T-wave amplitude or T wave to R wave ratio although the total serum calcium concentration showed an inverse relation with T wave amplitude (19). Thus, it was concluded that hemodialysis patients with hyperkalemia may not show the usual ECG alterations, probably due to fluctuations in serum calcium concentration (19).

It must be noted, however in our study, that some ECG changes suggestive of hyperkalemia (wide QRS, peaked-T waves, 1st degree AV-block and bradycardia) were significantly more prevalent in the severely hyperkalemic group. Although there wasn't a significant difference between the frequency of ECG alterations suggesting hyperkalemia in normokalemic and moderately hyperkalemic patients, the number of ECG alterations suggestive of hyperkalemia simultaneously present increased with the degree of serum potassium elevation. These findings are in line with a previous report on the higher frequency of ECG changes with increasing potassium levels (25). Peaked T waves are considered to be the typical earliest ECG signs of elevated serum potassium levels (16, 25, 26). In our study, peaked T-wave was the second most common ECG manifestation among severely hyperkalemic patients, while wide QRS was the most common ECG change and significantly

more often found among all hyperkalemic patients compared to patients with normal potassium levels.

We examined the prevalence of four ECG abnormalities, whose association with hyperkalemia has been found to be equivocal according to previous studies. ST depression may be an ECG manifestation of hyperkalemia (61), but we did not detect a significant difference in the frequency of ST depression between normokalemic and hyperkalemic patients in our study. Atrial fibrillation is the most frequently found sustained arrhythmia in the elderly and most studies have found that lower potassium levels were associated with a higher risk of atrial fibrillation (62-64). According to the results of the prospective population-based Rotterdam study, participants with hypokalemia (< 3.5mml/l) had a higher risk of atrial fibrillation (62-64). This association was independent of age, gender, serum magnesium and other potential confounders (62-64). Our results showed, however, that atrial fibrillation was more prevalent in severely hyperkalemic patients compared to normokalemic patients. We attribute these results to the synergistic effect of two groups of diseases often present in patients with high potassium levels. Hyperkalemia and heart failure are common in chronic kidney disease and heart failure is often the cause of or caused by atrial fibrillation. Therefore, atrial fibrillation occurs not as the result of hyperkalemia but rather as the consequence of illnesses often associated with hyperkalemia.

Although shortening of the QTc interval in hyperkalemia has been reported in several investigations (61, 65), the possibility of prolonged QTc occurance in hyperkalemia has also been raised (66). The results of a Japanese study investigating sudden cardiac death in hemodialysis patients implied that shifting of electrolytes, such as potassium and calcium during hemodialysis caused rapid prolongation of the QT interval after hemodialyis, which may have resulted in the onset of ventricular arrhythmia and sudden cardiac death (66). In our study, prolonged QTc was more frequent in severely hyperkalemic patients compared to normokalemic patients. In fact, prolonged QTc was the only ECG alteration significantly more frequent in both moderately and severely hyperkalemic patients compared to the group with normal potassium levels. The high prevalence of heart failure in hyperkalemic patients and the effect of drugs on the length of QTc may contribute to these results, similarly to our observation regarding atrial fibrillation. Although the reasons underlying our findings need to be clarified, the results imply that prolonged QTc and atrial fibrillation could also draw attention to hyperkalemia, besides the more acknowledged ECG manifestations of hyperkalemia. It is important for clinicians to be aware of the changing trend (e.g. higher

prevalence of heart disease, frequent application of certain drugs) of the clinical presentations of hyperkalemic patients.

Our study has other implications. When we compared baseline data from patients in the normokalemic and hyperkalemic groups, CKD and comborbidities such as heart and liver failure were significantly more frequent in hyperkalemic patients. CKD and/or hemodialysis have been known to increase the likelihood of hyperkalemia (19, 25) and so patients suffering from renal failure are more at risk of developing potassium cardiotoxicity (10). Within a decade there were twice as many cases of chronic renal failure in the United States attributed to hypertension and diabetes mellitus (26). Hyperkalemia was observed in the predialysis blood testing of patients requiring hemodialysis in 10% of the cases (26). Mortality from hyperkalemia could be attributed to 3-5% of patients receiving dialysis (67). The rising number of patients with chronic renal disease is predicted to increase the number of cases with hyperkalemia (26). Patients from the geriatric population are particularly prone to developing hyperkalemia, due to age-related decline in glomerular filtration rate, impaired rennin-angiotensin-aldosterone axis, higher number of comorbidities and the consumption of multiple medications (68).

The pharmacological treatment of patients with different kinds of cardiovascular diseases may also contribute to the rising number of hyperkalemic patients. Patients with medical conditions such as Type 2 DM and congestive heart failure are often treated with medication such as ACE-inhibitors (26). The application of certain types of medication, including ACE-I, ARB and potassium-sparing diuretics has been associated with an increased number of hyperkalemia-related hospitalizations and mortality (5, 69-71). Diuretics are among the most frequently prescribed drugs. Following the publication of the Randomized Aldactone Evaluation Study (RALES), for example, an increasing number of patients were hospitalized for hyperkalemia, which was thought to be the consequence of the more frequent prescription of spironolactone (26). In a Swiss cross-sectional analysis of patients presenting to the Emergency Room, it was demonstrated that the prevalence of hyperkalemia was linked to the number of diuretic agents taken by patients (69). In this study, all types of diuretics were associated with an increased prevalence of hyperkalemia (69). Hyperkalemia also often occurs as a consequence of drug-drug interactions such as due to the application of ACE-inhibitors with potassium-sparing diuretics (72).

In keeping with these earlier reports, we found in our study that the application of these types of drugs was also more common in patients with elevated potassium levels. Our data underline the importance of regular monitoring of electrolytes in patients taking hyperkalemia-inducing medication, preferably already in non-urgent situations within the primary care setting since ECG diagnosis of hyperkalemia is uncertain.

To our knowledge, this study is the first to investigate ECG alterations suggestive of hyperkalemia in a large number of patients with normal potassium levels. Besides supporting evidence for the unreliability of ECG diagnosis in hyperkalemia, our results show that a fourth of normokalemic patients also exhibit ECG alterations suggestive of hyperkalemia. This indicates that treatment of suspected hyperkalemia in the prehospital setting, prior to laboratory confirmation of potassium levels, may not be prudent. Although it has been suggested that initiation of life-saving treatment with calcium in suspected hyperkalemia prior to laboratory confirmation of hyperkalemia would be advisable, we disagree with this proposition (73). Investigations have shown, that the empiric treatment of hyperkalemia based on ECG alone was predicted to lead to the mistreatment of at least 15% of patients (59) and treatment decisions should not depend only on the presence of ECG alterations (25).

Limitations:

Our study has several limitations. The normokalemic (control) group and hyperkalemic group were not matched regarding age, medication and comorbidites. This was to be expected, however, as this investigation was a cross-sectional study of patients admitted to emergency care. The interpretation of ECGs may be another confounding factor, since a number of ECG alterations can be due to other causes than hyperkalemia or alternatively, ECG changes due to other conditions may mask signs of hyperkalemia. We argue, however, that in the prehospital, emergency setting information regarding medication and previous illnesses is not readily available to the caregiver and therefore, he or she must make decisions regarding diagnosis and treatment with none or very limited information. Another limitation of our study is that although the investigation was conducted on a relatively large number of patients, a larger-scale study examining the ECG alterations suggestive of hyperkalemia in normokalemic patients would be needed to confirm our results.

Our findings imply, what previous studies have suggested, that the ECG is not a reliable tool in the diagnosis of hyperkalemia. To this, our study adds valuable information by

demonstrating that a minority of patients with normal potassium levels may also exhibit ECG alterations considered to be typical for hyperkalemia. These results underline the importance of accurate laboratory-confirmed diagnosis of hyperkalemia prior to initiation of treatment. Nevertheless, since ECG alterations suggestive of hyperkalemia are more frequent in hyperkalemic patients, any change in the ECG attributable to hyperkalemia should draw attention to a potentially life threatening condition, in the prehospital emergency setting, especially in periarrest situations.

5.2   Discussion related to the "Case report of V.b.bosniensis envenomation"

Although snakebites are relatively rare in Hungary, their medical importance is unquestionable, since envenomation can cause severe symptoms and can even have life-threatening effects. Hospital admission may be delayed due to the remoteness of certain subspecies' habitats (74). Routine antivenom administration, without necessary individualisation of therapy due to the lack of information regarding the characteristics of the given snakes' venom may expose patients to higher risks of complications (74). Studies of neurotoxicity following snakebites are challenging, since there are large differences between individual patients in the clinical manifestations following envenoming of particular species. Comparing results from different studies is difficult since there is no uniform description or grading scale of neuromuscular weakness. The majority of our knowledge regarding snakebites from the literature comes from case reports.

Our case report focuses on the clinical presentation of a particular *V. b. bosniensis* bite which occurred in South-Western Hungary, the neurotoxic features of which resulted in the same peripheral neuromuscular paralytic symptoms that are typical of humans bitten by vipers in Southern and South-Eastern Europe. However, certain characteristics of our case differed from the common features of the European *Vipera* spp. envenomings.

The immediate local burning pain the patient experienced indicated that venom had been injected, athough *V. b. bosniensis* bites can be relatively painless (74). The minimal hematoma was consistent with the previously reported local symptoms in the Bulgarian as well as the South-Western Hungarian and Northern Croatian cases (74, 75). Relatively mild local venom effects characterizing the envenomings by these adders have already been

described by Reuss (47). Minimal local swelling with prolonged and marked systemic symptoms is atypical for the bites of the other European *Vipera* spp. Mild local symptoms cannot exclude moderate and severe envenomings caused by *V. b. bosniensis*, as is illustrated by our case.

In other cases, the local symptom of edema, which may be considered mild compared to systemic symptoms, can prove life-threatening. A previous case report described how the envenomation by *V. berus* of a patient, bitten on the tongue compromised the patient's airway causing severe hypoxemia, circulatory failure and an impaired level of consciousness (76).

The early onset dizziness and perspiration were probably due to anxiety and sympathetic overactivity. Psychological trauma often occurs after venomous snakebites (77). Nausea, vomiting and diarrhoea develop frequently in *V. berus* envenomings and are considered to be an early "anaphylactoid reaction" (39). The intensity and repeated occurrence of these symptoms indicate severe envenoming (77) just as in our case. Stomach ache and abdominal discomfort are commonly experienced and are often followed by diarrhoea (40). In case of extremely intensive pain, venom-induced acute abdominal catastrophe can be suspected (39). Our patient had painful abdominal guarding followed by colic and diarrhoea without any abdominal complications. All gastrointestinal symptoms ceased promptly and completely after antivenom administration. Similar abdominal symptoms were reported in a Bulgarian *V. b. bosniensis* envenoming (74).

Cardiovascular venom effects are the most commonly encountered features of *V. berus* envenomings in the whole European distribution range of the species. Arterial hypotension is a significant systemic manifestation of *V. b. berus* bites (39, 40, 78) but is also a known feature of *V. b. bosniensis* envenomings (75). However, envenomed patients may develop high blood pressure after being bitten by specimens belonging to certain populations of both subspecies (75, 79, 80). Hypotension, as well as hypertension often develop in the first two hours of the envenoming, and may be transient, persistent and/or recurrent (39, 75, 79-81). Our patient's transient high blood pressure might have been related to venom effects. The patient's blood pressure was normal (120/80 mmHg) initially (the patient took telmisartan in that morning) but then it suddenly increased, and this was followed by further episodes of high blood pressure during the course of the envenoming (in the early phase: 120/80-165/105 mmHg, and during hospitalization: 115/85-140/70 mmHg).

Venom of *V. b. berus* is considered potentially cardiotoxic (82) and cardiac complications are often recorded in such envenomings (39, 40, 78, 80). Arrhythmias are known to occur in those bitten by *V. b. bosniensis*. Reuss was the first to mention clinically significant arrhythmias and heart block in severe cases (75). The wide range of cardiac manifestations following the bite of both subspecies suggests that the transient horizontal ST depression and tachycardia detected in the case of our patient may have been due to the effect of the venom.

Neurotoxicity may be expected following the bite of specimens from certain populations of *V. b. berus* in the Carpathian Basin (79, 83) and *V. b. bosniensis* (47, 48, 74, 75, 84). In *V. b. bosniensis* envenomings, peripheral neurotoxicity involving mainly cranial nerve disturbances and gait incoordination are typical neurological manifestations (74, 75). In the case series reported by Westerström et al, diplopia, ptosis were described, whereas Častven (84) reported bulbar paralysis following Serbian *V. b. bosniensis* bites. These neurological signs and symptoms have been attributed to venom phospholipase A$_2$s (PLA$_2$s) (85). Complete or partial third nerve (oculomotor) palsy may occur, with symptoms of ophtalmoplegia due to the neurotoxic effect of the venom on the superior, medial and inferior rectus, inferior oblique and levator palpebrae superioris muscles of the eye. Ptosis is often associated with either partial or complete ophthalmoplegia, which are frequently diagnosed not only in *V. b. bosniensis* envenomings (74, 75) but also following the bites of specimens belonging to neurotoxic populations of *V. ammodytes* in Croatia, Bulgaria, and Slovenia, and *V. aspis* in France and Italy, respectively (41, 86-89). Snakebite neurotoxicity causes typical descending neuromuscular paralysis in humans (90). Extraocular muscles are affected earlier than skeletal muscles by venom neurotoxins presumably because of the peculiar structure of their neuromuscular junction and muscle-nerve ratio (90). Envenomed patients may show ataxic nystagmus in both lateral directions (91). This unique clinical sign of snakebite neurotoxicity combined with complete extraocular muscle palsy, was observed in our case.

Previously, a report described the case of a young man bitten on the forehead by a European adder (92). The resulting edema and petechial haemorrhages resolved after a few days but unilateral facial frontal paresis and ptosis persisted, Three weeks after the snake bite facial frontal paresis was still present and elecotromyography of the muscle initiated spontaneous fibrillation. Furthermore, unilateral ptosis was still present one year after the bite (92).

Due to the weakness of the facial and extraocular muscles in our patient the individual muscle fibers failed to contract intermittently, thereby producing signs of neuromuscular block on sfEMG. This finding adds a valuable piece of information to the medical literature of snakebites, as the available data about sfEMG studies performed in patients showing neuromuscular paralysis following snakebite is quite limited.

If the snake's venom contains prejunctional neurotoxic PLA_2s, the neuromuscular paralysis develops slowly and takes longer to recover (93). These patients show poor response or resistance to antivenom therapy and acetylcholinesterase inhibitors (94). Nevertheless, in our case there was a compelling urge to use antivenom therapy with respect to the massive gastrointestinal symptoms and the ECG changes. According to previous reports, edrophonium (Tensilon test) can be used to prognosticate the response to treatment with the longer-acting neostigmine, if the neuromuscular blockade caused by the venom is post-synaptic (95). In the case of our patient, neostigmine was applied on the day following the bite in an attempt to ameliorate the neurological signs and symptoms. The patient also received atropine to avoid the potential side effects of neostigmine. The slowly evolving and prolonged neurologic manifestations, the lack of benefit from the antivenom and neostigmine therapy applied with regards to the neurotoxicity, strongly suggest that the venom of the South-Western Hungarian *V. b. bosniensis* contained prejunctional neurotoxic PLA_2(s), as suggested previously by Malina et al. (79). The neurotoxic effects were observed in our patient. Interestingly, according to a most recent investigation, in which the toxicological profile of *V. aspis* and *V. berus* venoms were tested *in vivo* in mice, it was shown that both venoms contain enzymatically active PLA_2, but only the venom of *V. aspis* was demonstrated to be neurotoxic (29). The effect of the neurotoxin was shown to be due to the degeneration of peripheral nerve terminals at the neuromuscular junction and *V. berus* venom was shown to cause a haemorrhagic effect (29). The explanation for the discrepancy between the results of this study and previous case reports, along with our patient's case is currently unclear but could be explained by two possible hypotheses; one being the experimental characteristic (experiments in mice) of this recent study by Zanetti et al. (29), as opposed to human cases of snake bites, and the other hypothesis being that differences between neurotoxicity were found due to intraspecies venom variability.

Viper Venom Antitoxin was given to the patient in our case. To date there are very few preclinical comparative data and no randomised controlled trials evaluating the efficacy of

antivenoms against different vipera species. (96) The previous review on antivenoms suggested the efficacy of *Zagreb, ViperFAV* and *Viper Tab* in clinical studies. (96) Based on the earlier case described by Malina et al. (79) as well as our patient's case, it would be prudent to consider the use of polivalent antivenoms, such as *Zagreb* in the antivenom therapy of *V. b. bosniensis* snake bites, due to the high venom component variability between the individual snakes.

Based on the new classification of *Vipera spp*. envenomings (97), our patient's case can be categorized as moderate or severe, although, certain atypical features made grading difficult.

The laboratory findings were compatible with those usually seen in *V. berus* envenomings. Slight abnormalities in the haemostatic parameters combined with mild local symptoms were consistent with the previously reported cases (75) and similar to the Eastern Hungarian neurotoxic *V. b. berus* envenomings (79, 83). In Bulgaria, a severe neurotoxic *V. b. bosniensis* bite resulted in a slightly reduced haematocrit value (39%), leukocytosis (absolute neutrophil count: 12.2 G/L) and elevated blood glucose level only (Boyan Petrov, pers. comm., 2017; without full details by Westerström et al., (74)). Haematological changes of any kind were not reported in neurotoxic bites of *V. b. bosniensis* in Serbia (84). Taking into account the clinical significance of venom composition variability not only between the different adder populations but also at the intra-populational level as it was described in *V. b. berus* (44), the potential existence of venom composition differences is not negligible in South-Western Hungarian adders, either. Additionally, an inverse correlation can be probable between the neurotoxic and the proteolytic activity and/or protease content of venom in case of *V. b. bosniensis*, similarly to the specimens of a particular, Eastern Hungarian, neurotoxic *V. b. berus* population (44).

Our case study describes the consequences of *V. b. bosniensis* bite, which occurred in the northernmost geographical distribution range of the taxon. Certain uncommon features of this case – i.e. minor local venom effects combined with prolonged and marked systemic symptoms and almost normal absolute neutrophil count – raise the issue of venom component variability within the geographical range of the Balkan adder and also between individual animals within the same population. On the other hand, classical signs and symptoms of descending neuromuscular paralysis associated with snakebite neurotoxicity developed in our patient affecting the 3rd, 4th, and 6th cranial nerves innervating the eye lid, the extraocular

and the facial muscles. The slowly developing and prolonged neurological manifestations and their unresponsiveness to acetylcholinesterase inhibitor and antivenom therapy indicate the presence of prejunctional PLA_2(s) in the venom of South-Western Hungarian adders. Our observations underline the importance of venom component variability of individuals within the same viper population, which should be taken into careful consideration when choosing the most appropriate antivenom therapy.

6   Conclusions

1. Hyperkalemic patients were older than patients in the normokalemic (control) group in our study. Almost a third (29.6%) of the hyperkalemic patients suffered from chronic kidney disease (CKD), while only 8.8% of the normokalemic patients had CKD. A significantly higher percentage of hyperkalemic patients took angiotensin receptor blockers, angiotensin coverting enzyme inhibitors, non steroid analgesics, potassium supplements, and diuretics than normokalemic patients. Comorbidities, such as heart failure, diabetes mellitus, liver failure, sepsis, cancer and dehydration were also significantly more prevalent in hyperkalemic patients. Mortality within 72 hours of admission was significntly higher (13.3%) in the hyperkalemic group compared to only 2.4% of normokalemic patients.

2. 24% of normokalemic patients and 46% of patients with moderate or severe hyperkalemia had ECG alterations suggestive of hyperkalemia. 29% of severely hyperkalemic patients had no ECG changes indicative of hyperkalemia whatsoever.

3. Significantly more patients with severe hyperkalemia had wide QRS, bradycardia, peaked T-waves and 1st degree AV block compared to normokalemic patients. There was no significant difference in the frequency of ECG alterations suggestive of hyperkalemia between the normokalemic and the moderately hyperkalemic groups. When normokalemic patients were compared to all (moderately + severely) hyperkalemic patients, we found that wide QRS was the only ECG alteration significantly more frequent in all hyperkalemic patients compared to normokalemic patients.

4. Prolonged QTc was the only ECG alteration which was significantly more prevalent in both patients with moderate and severe hyperkalemia compared to patients with normokalemia. There was no significant difference regarding the frequency of ST depression between patients with normal or increased levels of potassium. Atrial fibrillation was significantly more frequent in severely hyperkalemic patients compared to normokalemic patients. The higher prevalence of both prolonged QTc

and atrial fibrillation in hyperkalemic patients raises the suspicion of covariance: that the simultaneous higher occurance of heart failure and associated drug treatment may be responsible for our observations.

5. With the elevation of potassium levels from moderate to severe hyperkalemia, atrial fibrillation, I^o AV block, wide QRS and peaked T waves were present more frequently, therefore a positive correlation could be detected between the frequency of these ECG alterations and the severity of hyperkalemia.

6. Our results imply that the ECG is not a reliable tool in the diagnosis of hyperkalemia, since severely hyperkalemic patients may have no ECG manifestations at all, while patients with normal potassium levels may also exhibit ECG alterations considered to be typical for hyperkalemia.

   These findings underline the importance of accurate laboratory-confirmed diagnosis of hyperkalemia prior to initiation of treatment.

7. The envenoming by *Vipera b. bosniensis* of the patient in our case report caused characteristically mild local symptoms at the site of the bite but the prolonged and marked systemic symptoms, implying severe envenoming is not characteristic of envenomings caused by this *Vipera* ssp. Systemic symptoms included dizziness, vomiting, diarrhea, abdominal guarding, transient blood pressure elevations, transient horizontal ST depression on the ECG and symptoms of neurotoxicity.

8. We observed the unique clinical signs of snakebite neurotoxicity, complete extraocular muscle palsy and ataxic nystagmus, in our patient.

9. Using sfEMG, we found, that the individual muscle fibers in the facial and extraocular muscles in our patient failed to contract intermittently, which indicated that the snake venom induced neuromuscular blockage.

10. Due to the pronounced neurological disturbances and the lack of benefit from the antivenom and acetylcholinesterase inhibitor treatment and based on previous descriptions in the literature, we hypothesized that the observed neuromuscular blockage was due to the prejunctional PLA$_2$ (s) present in the venom of South-Western Hungarian adders.

11. Our case report of *Vipera berus bosniensis* envenoming implies that non-characteristic features of snakebites may be expected due to the venom component variability within a population of *Vipera* ssp. Therefore, despite mild local symptoms at the site of the snake bite, healthcare professionals should be prepared for the treatment of moderate to severe systemic symptoms in patients following South-Western Hungarian adder envenoming.

The particular type of antivenom treatment should also be carefully selected. Based on the experience of our case, and supported by others, due to venom component variability, the use of *polyvalent* antivenom treatment should be considered.

The study regarding the common medical condition of hyperkalemia and the case report of the relatively rare case of snake envenoming aptly demonstrate the challenges of decision-making in emergency medicine. In spite of the overcrowded workflow of the emergency department keen attention needs to be paid to each patient and priority given based on the urgency of each case.

Limitations

The findings of this thesis have to be considered in light of its limitations. The first is that out of the numerous different emergency cases we decided to choose one common and one rare medical condition instead of others. The second limitation concerns the methodology of the investigations. The study on hyperkalemic ECG alterations examined a larger number of patients, however, the second report illustrated the case of only one patient.

7 References

1.   (EuSEM) ESfEM. Az Európai sürgősségi orvostan alapelvei:
http://msotke.hu/downloads/szakmai/eusem_policy.pdf; 2013 [

2.   Truhlar A, Deakin CD, Soar J, Khalifa GE, Alfonzo A, Bierens JJ, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. Resuscitation. 2015;95:148-201.

3.   Wilson MH, Habig K, Wright C, Hughes A, Davies G, Imray CH. Pre-hospital emergency medicine. (1474-547X (Electronic)).

4.   Wiler JL, Gentle C Fau - Halfpenny JM, Halfpenny Jm Fau - Heins A, Heins A Fau - Mehrotra A, Mehrotra A Fau - Mikhail MG, Mikhail Mg Fau - Fite D, et al. Optimizing emergency department front-end operations. (1097-6760 (Electronic)).

5.   Alharbi FF, Souverein PC, de Groot MCH, Blom MT, de Boer A, Klungel OH, et al. The impact of serum potassium-influencing antihypertensive drugs on the risk of out-of-hospital cardiac arrest: A case-control study. British journal of clinical pharmacology. 2017;83(11):2541-8.

6.   Bardai A, Amin AS, Blom MT, Bezzina CR, Berdowski J, Langendijk PN, et al. Sudden cardiac arrest associated with use of a non-cardiac drug that reduces cardiac excitability: evidence from bench, bedside, and community. European heart journal. 2013;34(20):1506-16.

7.   Huikuri HV. Implantable cardioverter-defibrillator therapy and the total burden of sudden cardiac death. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2009;11(12):1574.

8.   Moore ML, Bailey RR. Hyperkalaemia in patients in hospital. The New Zealand medical journal. 1989;102(878):557-8.

9.   Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. The American journal of medicine. 1995;98(6):575-86.

10.   Paice B, Gray JM, McBride D, Donnelly T, Lawson DH. Hyperkalaemia in patients in hospital. British medical journal (Clinical research ed). 1983;286(6372):1189-92.

11.   DeBehnke DJ, Hilander SJ, Dobler DW, Wickman LL, Swart GL. The hemodynamic and arterial blood gas response to asphyxiation: a canine model of pulseless electrical activity. Resuscitation. 1995;30(2):169-75.

12.   Alvo M, Warnock DG. Hyperkalemia. The Western journal of medicine. 1984;141(5):666-71.

13.   Kunis CL, Lowenstein J. The emergency treatment of hyperkalemia. The Medical clinics of North America. 1981;65(1):165-76.

14.   Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. North American journal of medical sciences. 2013;5(4):255-9.

15.   Soar J, Perkins GD, Abbas G, Alfonzo A, Barelli A, Bierens JJ, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. Resuscitation. 2010;81(10):1400-33.

16.   Diercks DB, Shumaik GM, Harrigan RA, Brady WJ, Chan TC. Electrocardiographic manifestations: electrolyte abnormalities. The Journal of emergency medicine. 2004;27(2):153-60.

17.   Dittrich KL, Walls RM. Hyperkalemia: ECG manifestations and clinical considerations. The Journal of emergency medicine. 1986;4(6):449-55.

18.   Martinez-Vea A, Bardaji A, Garcia C, Oliver JA. Severe hyperkalemia with minimal electrocardiographic manifestations: a report of seven cases. Journal of electrocardiology. 1999;32(1):45-9.

19.   Aslam S, Friedman EA, Ifudu O. Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2002;17(9):1639-42.

20.   Tzamaloukas AH, Avasthi PS. Temporal profile of serum potassium concentration in nondiabetic and diabetic outpatients on chronic dialysis. American journal of nephrology. 1987;7(2):101-9.

21.   Levis JT. ECG Diagnosis: Hyperacute T Waves. The Permanente journal. 2015;19(3):79.

22.   Mattu A, Brady WJ, Robinson DA. Electrocardiographic manifestations of hyperkalemia. The American journal of emergency medicine. 2000;18(6):721-9.

23. Kumar K, Biyyam M, Singh A, Bajantri B, Tariq H, Nayudu SK, et al. Transient Left Bundle Branch Block due to Severe Hyperkalemia. Cardiology research. 2017;8(2):77-80.

24. Campistol JM, Almirall J, Montoliu J, Revert L. Electrographic alterations induced by hyperkalaemia simulating acute myocardial infarction. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 1989;4(3):233-5.

25. Montague BT, Ouellette JR, Buller GK. Retrospective review of the frequency of ECG changes in hyperkalemia. Clinical journal of the American Society of Nephrology : CJASN. 2008;3(2):324-30.

26. Freeman K, Feldman JA, Mitchell P, Donovan J, Dyer KS, Eliseo L, et al. Effects of presentation and electrocardiogram on time to treatment of hyperkalemia. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2008;15(3):239-49.

27. Ryuge A, Nomura A, Shimizu H, Fujita Y. Warning: The ECG May Be Normal in Severe Hyperkalemia. Internal medicine (Tokyo, Japan). 2017;56(16):2243-4.

28. Acker CG, Johnson JP, Palevsky PM, Greenberg A. Hyperkalemia in hospitalized patients: causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. Archives of internal medicine. 1998;158(8):917-24.

29. Zanetti G, Duregotti E, Locatelli CA, Giampreti A, Lonati D, Rossetto O, et al. Variability in venom composition of European viper subspecies limits the cross-effectiveness of antivenoms. Scientific reports. 2018;8(1):9818.

30. Beer E, Putorti F. Dysphonia, an uncommon symptom of systemic neurotoxic envenomation by Vipera aspis bite. Report of two cases. Toxicon : official journal of the International Society on Toxinology. 1998;36(5):697-701.

31. Puig J, Vilafranca M, Font A, Closa J, Pumarola M, Mascort J. Acute intrinsic renal failure and blood coagulation disorders after a snakebite in a dog. The Journal of small animal practice. 1995;36(7):333-6.

32. Korsós Z. Postglacial history of the reptile fauna in the Carpathian Basin. in: Forró L. (Ed.), Development of the fauna in the Carpathian Basin. Magyar Természettudományi Múzeum, Budapest. 2007:pp. 283-96.

33. Marián M. Occurrence of the melanistic form of the common adder (Vipera berus var. prester L.) in Somogy County. Rippl-Rónai Múzeum, Kaposvár. 1952:pp. 1-2. .

34. Dudich E. Faunistic notes. Állattani Közlemények. 1928;25:44.

35.   Marián M. Some data concerning the distribution in Com. Somogy of the Common viper (Vipera b. berus L.). Ann hist-nat Mus Nat Hung. 1956;7:463-8.

36.   Anonymous. Adder hunting. Magyar Vadász. 1964;17:12.

37.   Organization WH. Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Geneva, Annex 1. 2016:pp. 113-30.

38.   Malina T, Babocsay G, Krecsak L, Schuller P, Zacher G, Vasas G. [An overview on envenomings inflicted by the Common adder (Vipera berus) and their treatment in Hungary. Facts and beliefs -- part I]. Orvosi hetilap. 2012;153(28):1092-105.

39.   Warrell DA. Treatment of bites by adders and exotic venomous snakes. BMJ (Clinical research ed). 2005a;331(7527):1244-7.

40.   Karlson-Stiber C, Salmonson H, Persson H. A nationwide study of Vipera berus bites during one year-epidemiology and morbidity of 231 cases. Clinical toxicology (Philadelphia, Pa). 2006;44(1):25-30.

41.   Ferquel E, de Haro L, Jan V, Guillemin I, Jourdain S, Teynie A, et al. Reappraisal of Vipera aspis venom neurotoxicity. PloS one. 2007;2(11):e1194.

42.   Daltry JC, Ponnudurai G, Shin CK, Tan NH, Thorpe RS, Wuster W. Electrophoretic profiles and biological activities: intraspecific variation in the venom of the Malayan pit viper (Calloselasma rhodostoma). Toxicon : official journal of the International Society on Toxinology. 1996;34(1):67-79.

43.   Shashidharamurthy R, Jagadeesha DK, Girish KS, Kemparaju K. Variations in biochemical and pharmacological properties of Indian cobra (Naja naja naja) venom due to geographical distribution. Molecular and cellular biochemistry. 2002;229(1-2):93-101.

44.   Malina T, Krecsak L, Westerstrom A, Szeman-Nagy G, Gyemant G, M MH, et al. Individual variability of venom from the European adder (Vipera berus berus) from one locality in Eastern Hungary. Toxicon : official journal of the International Society on Toxinology. 2017;135:59-70.

45.   Malina T, editor Clinical picture of the envenomings by different populations of the Common adder (Vipera berus) in Hungary. 17th Congress of the European Section of the International Society on Toxinology; 2011 2011/09/11; Valencia, Spain. Program and Abstract Book, pp. 32.

46.   Reid HA. Adder bites in Britain. British medical journal. 1976;2(6028):153-6.

47.   Reuss FAT. Observations on four species of European Toxicophidia. In: C R XII Congr Int Zool–Lisabonne 1937:1787-804.

48. Reuss T. Über eine neurotoxische Otterngruppe Europas, Mesocoronis 1927, und über ihre Stellung unter den Solenoglyphen der Welt. Glasnik Zemalsk Mus Bosn Herc. 1930;42:57-114 +3 tables + 1 map, Pls. 1-6.

49. Jelič D, Ajtić, R., Sterijovski, B., Crnobrnja-Isailović, J., Lelo, S., Tomović, L. Distribution of the genus Vipera in the Western and Central Balkans (Squamata: Serpentes: Viperidae). Herpetozoa. 2013;25:109-32.

50. Fejérváry G. About our snakes. Az Erdő. 1934;4-5:1-9.

51. Ranawaka UK, Lalloo DG, de Silva HJ. Neurotoxicity in snakebite--the limits of our knowledge. PLoS neglected tropical diseases. 2013;7(10):e2302.

52. Fagerlund MJ, Eriksson LI. Current concepts in neuromuscular transmission. British journal of anaesthesia. 2009;103(1):108-14.

53. Martyn JA, Fagerlund MJ, Eriksson LI. Basic principles of neuromuscular transmission. Anaesthesia. 2009;64 Suppl 1:1-9.

54. Shear TD, Martyn JA. Physiology and biology of neuromuscular transmission in health and disease. Journal of critical care. 2009;24(1):5-10.

55. Székely M. Kórélettani alapok. In: Székely M, editor.2018. p. 147-8.

56. Webster A, Brady W, Morris F. Recognising signs of danger: ECG changes resulting from an abnormal serum potassium concentration. Emergency medicine journal : EMJ. 2002;19(1):74-7.

57. Gumz ML, Rabinowitz L, Wingo CS. An Integrated View of Potassium Homeostasis. The New England journal of medicine. 2015;373(18):1787-8.

58. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: advanced challenges in resuscitation: section 1: life-threatening electrolyte abnormalities. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation. 2000;102(8 Suppl):I217-22.

59. Wrenn KD, Slovis CM, Slovis BS. The ability of physicians to predict hyperkalemia from the ECG. Annals of emergency medicine. 1991;20(11):1229-32.

60. Rafique Z, Aceves J, Espina I, Peacock F, Sheikh-Hamad D, Kuo D. Can physicians detect hyperkalemia based on the electrocardiogram? The American journal of emergency medicine. 2019.

61. Levis JT. ECG diagnosis: hyperkalemia. The Permanente journal. 2013;17(1):69.

62. Krijthe BP, Heeringa J, Kors JA, Hofman A, Franco OH, Witteman JC, et al. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. International journal of cardiology. 2013;168(6):5411-5.

63.   Yan L, Jiang T, Yang X, Xu M. Spontaneous conversion of atrial fibrillation caused by severe hyperkalemia: A case report. Medicine. 2018;97(15):e0442.

64.   Liu R, Chang Q, Liu A. Permanent atrial fibrillation: Special electrocardiogram in hyperkalemia. International journal of cardiology. 2016;215:519-20.

65.   Khan IA. Long QT syndrome: diagnosis and management. American heart journal. 2002;143(1):7-14.

66.   Joki N, Tokumoto M, Takahashi N, Nishimura M. Current Perspectives on Sudden Cardiac Death in Hemodialysis Patients. Contributions to nephrology. 2018;196:5-12.

67.   Ahmed J, Weisberg LS. Hyperkalemia in dialysis patients. Seminars in dialysis. 2001;14(5):348-56.

68.   McIntyre WF, Femenia F, Arce M, Perez-Riera AR, Baranchuk A. Importance of early electrocardiographic recognition and timely management of hyperkalemia in geriatric patients. Experimental and clinical cardiology. 2011;16(2):47-50.

69.   Arampatzis S, Funk GC, Leichtle AB, Fiedler GM, Schwarz C, Zimmermann H, et al. Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. BMC medicine. 2013;11:83.

70.   Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. The New England journal of medicine. 2004;351(6):543-51.

71.   Centers for Disease C, Prevention. State-specific trends in chronic kidney failure--United States, 1990-2001. MMWR Morb Mortal Wkly Rep. 2004;53(39):918-20.

72.   Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. Jama. 2003;289(13):1652-8.

73.   Riccardi A, Tasso F, Corti L, Panariello M, Lerza R. The emergency physician and the prompt management of severe hyperkalemia. Internal and emergency medicine. 2012;7 Suppl 2:S131-3.

74.   Westerstrom A, Petrov B, Tzankov N. Envenoming following bites by the Balkan adder Vipera berus bosniensis - first documented case series from Bulgaria. Toxicon : official journal of the International Society on Toxinology. 2010;56(8):1510-5.

75.   Malina T, Krecsak L, Jelic D, Maretic T, Toth T, Sisko M, et al. First clinical experiences about the neurotoxic envenomings inflicted by lowland populations of the Balkan adder, Vipera berus bosniensis. Neurotoxicology. 2011;32(1):68-74.

76.   Hoegberg LC, Jessen CL, Lambertsen K, Stensballe J. Common adder bite to the tongue causing life threatening toxicity from airway compromise. Clinical toxicology (Philadelphia, Pa). 2010;48(4):397-8.

77.   Persson H. Pathophysiology and treatment of envenomation by European vipers. in: Gopalakrishnakone, P., Faiz, M.A., Fernando, R., Gnanathasan, C.A., Habib, A.G., Yang, C.-C. (Eds.). Clinical Toxinology in Asia Pacific and Africa Springer Netherlands. 2015:pp. 1-15.

78.   Magdalan J, Trocha M, Merwid-Lad A, Sozanski T, Zawadzki M. Vipera berus bites in the Region of Southwest Poland--a clinical analysis of 26 cases. Wilderness & environmental medicine. 2010;21(2):114-9.

79.   Malina T, Krecsak L, Warrell DA. Neurotoxicity and hypertension following European adder (Vipera berus berus) bites in Hungary: case report and review. QJM : monthly journal of the Association of Physicians. 2008;101(10):801-6.

80.   Garkowski A, Czupryna P, Zajkowska A, Pancewicz S, Moniuszko A, Kondrusik M, et al. Vipera berus bites in Eastern Poland--a retrospective analysis of 15 case studies. Annals of agricultural and environmental medicine : AAEM. 2012;19(4):793-7.

81.   Warrell DA. Injuries, envenoming, poisoning, and allergic reactions caused by animals. Warrell, DA, Cox, TM, Firth, JD (Eds), Oxford Textbook of Medicine Oxford University Press Inc, Oxford, UK 4. 2003:923-46.

82.   Latinovic Z, Leonardi A, Sribar J, Sajevic T, Zuzek MC, Frangez R, et al. Venomics of Vipera berus berus to explain differences in pathology elicited by Vipera ammodytes ammodytes envenomation: Therapeutic implications. Journal of proteomics. 2016;146:34-47.

83.   Malina T, Babocsay G, Krecsak L, Erdesz C. Further clinical evidence for the existence of neurotoxicity in a population of the European adder (Vipera berus berus) in eastern Hungary: second authenticated case. Wilderness & environmental medicine. 2013;24(4):378-83.

84.   Častven J. Snakebites in Vršac Mountain Area. GEA. 2004;4:9.

85.   Harris JB, Scott-Davey T. Secreted phospholipases A2 of snake venoms: effects on the peripheral neuromuscular system with comments on the role of phospholipases A2 in disorders of the CNS and their uses in industry. Toxins. 2013;5(12):2533-71.

86.   Luksic B, Bradaric N, Prgomet S. Venomous snakebites in southern Croatia. Collegium antropologicum. 2006;30(1):191-7.

87.   Stoyanova V, Aleksandrov R, Lukarska M, Duhalov D, Atanasov V, Petrova S. Recognition of Vipera ammodytes meridionalis neurotoxin vipoxin and its components using

phage-displayed scFv and polyclonal antivenom sera. Toxicon : official journal of the International Society on Toxinology. 2012;60(5):802-9.

88.   Sarc L, Sega S, Zidar J. Neurotoxicity caused by Vipera ammodytes bite: A case report. Clinical Toxicology, XXXIII International Congress of the EAPCCT 4. 2013:275.

89.   Lonati D, Giampreti A, Rossetto O, Petrolini VM, Vecchio S, Buscaglia E, et al. Neurotoxicity of European viperids in Italy: Pavia Poison Control Centre case series 2001-2011. Clinical toxicology (Philadelphia, Pa). 2014;52(4):269-76.

90.   Silva A, Hodgson WC, Isbister GK. Antivenom for Neuromuscular Paralysis Resulting From Snake Envenoming. Toxins. 2017;9(4).

91.   Warrell DA. Management of snake-bitten patient in hospital. in: Williams, D, Jensen S, Nimorakiotakis, B, Winkel KD (Eds), Venomous bites and stings in Papua New Guinea A treatment guide for health workers and doctors Australian Venom Research Unit, Melbourne, Australia. 2005b:pp. 245-69.

92.   Weinelt W, Sattler RW, Mebs D. Persistent paresis of the facialis muscle after European adder (Vipera berus) bite on the forehead. Toxicon : official journal of the International Society on Toxinology. 2002;40(11):1627-9.

93.   Jensen S. Symptoms and signs of snakebite in Papua New Guinea. in: Williams, D., Jensen S., Nimorakiotakis, B., Winkel K.D. (Eds.), Venomous bites and stings in Papua New Guinea. A treatment guide for health workers and doctors. Australian Venom Research Unit, Melbourne, Australia. 2005:pp. 86-101.

94.   Winkel KD, Nimorakiotakis, B., McGain, F., Williams, D. Anticholinesterase therapy. in: Williams, D, Jensen S, Nimorakiotakis, B, Winkel KD (Eds), Venomous bites and stings in Papua New Guinea A treatment guide for health workers and doctors Australian Venom Research Unit, Melbourne, Australia. 2005:pp. 211-7.

95.   Watt G, Theakston RD, Hayes CG, Yambao ML, Sangalang R, Ranoa CP, et al. Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja naja philippinensis). A placebo-controlled study. The New England journal of medicine. 1986;315(23):1444-8.

96.   Lamb T, de Haro L, Lonati D, Brvar M, Eddleston M. Antivenom for European Vipera species envenoming. Clinical toxicology (Philadelphia, Pa). 2017;55(6):557-68.

97.   Martin C, Nogue S. [Changes in viper bite poisonings]. Medicina clinica. 2015;144(3):132-6.

8   Publications

8.1   Publications related to the thesis

1. **Csaba Varga**; Zsolt Kalman; Aliz Szakall; Kata Drubits; Marton Koch; Robert Banhegyi; Tibor Olah; Eva Pozsgai; Norbert Fulop; Jozsef Betlehem.

ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients. BMC EMERGENCY MEDICINE DOI: 10.1186/s12873-019-0247-0

(IF: 1.39)

2. **Csaba, Varga** ; Tamás, Malina ; Viktória, Alföldi ; Gergely, Bilics ; Ferenc, Nagy ; Tibor, Oláh.

Extending knowledge of the clinical picture of Balkan adder (Vipera berus bosniensis) envenoming: The first photographically-documented neurotoxic case from South-Western Hungary. TOXICON 143 pp. 29-35. Paper: 10.1016/j. toxicon. 2017.12.053 , 7 p. (2018)

(IF: 2.352)

IF in the topic: 3.742

8.2   Oral and poster presentations related to the thesis

1. Varga, Csaba

Kígyómarások kapcsán észlelt neurotoxikus tünetegyüttes

In: Betlehem, J; Radnai, B; Deutsch, K; Bánfai, B; Pandur, A; Schiszler, B; Tóth, B; Bánfai-Csonka, H; Talabér, K; Köcse, T; Horváth, B

XIV. Pécsi Sürgősségi Napok: Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2019) pp. 35-35. , 1 p.

2. Kálmán Zs. ; Szakáll A.; Csupor K.; Juhász A.; Fülöp,N.; **Varga, Cs.**

Prevalence of iatrogenic hyperkalemia in the Emergency Department ICU

INTENSIVE CARE MEDICINE 40 : Suppl. 1 pp. S255-S255. Paper: 0955 (2014)

8.3 Other publications

1. Büki, A ; Barzó, P ; Demeter, B ; Kanizsai, P ; Ezer, E ; Tóth, P ; Horváth, P ; **Varga, C**
Baleseti agysérültek ellátásának irányelvei - 2017 [Guidelines for the treatment of traumatic brain injury-2017]. IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 70 : 7-8 pp. 223- 246. , 24 p. (2017)
(IF: 0.252)

2. **Varga, Csaba** ; Lelovics, Zsuzsanna ; Soós, Viktor ; Oláh, Tibor
Betegforgalmi trendek multidiszciplináris sürgősségi osztályon [Patient turnover in a multidisciplinary emergency department]. ORVOSI HETILAP 158 : 21 pp. 811-822. , 12 p. (2017)
(IF: 0.322)

3. Betlehem, József **; Varga, Csaba** ; Berényi, Tamás ; Oláh, András
A hazai sürgősségi ellátás szakdolgozói humánerőforrás ellátottsága [The national human resource supply in the emergency care] NÉPEGÉSZSÉGÜGY 93 : 1 pp. 44-50. , 7 p. (2015)

4. Radnai, Péter ; Szőts, Mónika ; Rádai, Ferenc ; Horváth, Gyula ; **Varga, Csaba** ; Fogas, János ; Szörényi, Péter ; Horváth, Zoltán ; Bajzik, Gábor ; Moizs, Mariann et al.
Az akut ischaemiás stroke neurointervenciós kezelésével szerzett kaposvári tapasztalataink [Neurointerventional treatment of acute ischemic stroke: the Kaposvár experience] IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 68: 7–8 pp. 252- 257. , 6 p. (2015)
(IF: 0.376)

5. **Varga, Csaba** ; Nagy, Ferenc ; Drubits, Katalin ; Lelovics, Zsuzsanna ; Varga, Győrfi Krisztina ; Oláh, Tibor
A sürgősségi ellátásban szédüléssel jelentkező betegek adatainak elemzése. [Analysis of patients applying for emergency treatment with vertigo related symptoms.] IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 67 : 5–6 pp. 193- 200. , 8 p. (2014)
(IF: 0.386)

6. **Varga, Csaba** ; Orbán, Sándorné ; Lelovics, Zsuzsanna ; Zádori, Péter ; Betlehem, József ; Fülöp, Norbert ; Oláh, Tibor

Az S-100B-proteinszint meghatározásának jelentősége a koponyasérültek sürgősségi ellátásában. [The importance of serum S-100B protein measurements in emergency care of traumatic head injury patients.] EGÉSZSÉG-AKADÉMIA 4 : 4 pp. 232-239. , 8 p. (2013)

7. **Varga, Csaba**

Jellemző sérülések közlekedési baleseteknél. VÉDELEM - KATASZTRÓFA- TŰZ- ÉS POLGÁRI VÉDELMI SZEMLE 8 : 6 pp. 25-27. , 3 p. (2001)

Cumulative IF: 5.078

8.4   Other publications, other oral and poster presentations not related to the thesis

1. **Varga, Csaba** ; Garábi, Beáta ; Kiss, Mariann

Miért nem figyelnek a gyerekek matek órán? [Why are not the children interested in maths?]

In: Betlehem, J; Radnai, B; Deutsch, K; Bánfai, B; Pandur, A; Schiszler, B XIII. Pécsi Sürgősségi Napok 2018. szeptember 21-22. Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2018) pp. 7-7. , 1 p.

2. **Varga, Csaba**

Hibák és szövődmények CPR kapcsán

In: László, István; Szabó, Zoltán; Fülesdi, Béla

Újraélesztés. Budapest, Magyarország: Medicina Könyvkiadó Zrt., (2018) pp. 421-434. , 14 p.

3. Doloczki, Örs ; Koch, Márton ; **Varga, Csaba**

Sepsis 6 protokoll adaptálása a SMKMOK Sürgősségi Betegellátó Centrumában

pp. 40-41. , 2 p. Magyar, Sürgősségi Orvostani Társaság 16. Magyar sürgősségi orvostani kongresszus program és összefoglalók. Budapest, Magyarország : Magyar Sürgősségi Orvostani Társaság, (2017)

4. **Varga, Csaba**

Tromboembóliák, antikoagulálás, sürgősségi ellátás pp. 22-22. , 1 p.

In: Betlehem, József; Radnai, Balázs; Deutsch, Krisztina; Bánfai, Bálint; Pandur, Attila; Schiszler, Bence XII. Pécsi Sürgősségi Napok: XII. Critical Care Days in Pécs : előadáskivonatok, absztraktok. Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2017) p. 47

5. **Varga, Csaba** ; Tóth, Kálmán ; Sánta, Lajos

Doktor úr, szorít a mellkasom, mintha abroncs lenne rajta!

In: Magyar, Sürgősségi Orvostani Társaság 5. Fehérvári Atherosclerosis Találkozó Budapest, Magyarország (2017) p. online

6. **Varga, Csaba**

Gondolatok a sürgősségi ellátás finanszírozásáról

In: Izbéki, Ferenc; Sárkány, Ágnes; Ebrahim, Soori 6. Fehérvári orvosnapok. Székesfehérvár, 2017. február 3–4. Programfüzet
Budapest, Magyarország : Remedicon, (2017) p. 62 pp. 14-15. , 2 p.

7. **Varga, Csaba** ; Kiss, Mariann ; Soós, Viktor ; Lelovics, Zsuzsanna

Multidiszciplináris sürgősségi osztályon megjelenő gyermekek epidemiológiai adatainak elemzése.

In: A Magyar Gyermekorvosok Társasága és a Magyar Sürgősségi Orvostani Társaság, I. Magyar Gyermek Sürgősségi Kongresszusa. Budapest, Magyarország : Magyar Gyermekorvosok Társasága, (2016) pp. 24-24. , 1 p.

8. **Varga, Csaba**

A kiterjesztett okleveles ápolói szerepkörök helye a hazai sürgősségi ellátásban

In: Oláh, András XII. Főiskolát és Egyetemet Végzett Ápolók Országos és Nemzetközi

Kongresszusa : részletes program és előadás kivonatok

Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2016)

pp. 42-42. , 1 p.

9. **Varga, Csaba** ; Soós, Viktor

Gondolatok a sürgősségi ellátás finanszírozásáról

In: Betlehem, József; Radnai, Balázs; Deutsch, Krisztina; Bánfai, Bálint; Pandur, Attila; Füge,

Kata XI. Pécsi Sürgősségi Napok [11th Critical Care Days in Pécs] : Részletes program és

előadáskivonatok [Final Program and Abstracts]. Pécs, Magyarország : Pécsi

Tudományegyetem, (2016) pp. 12-12. , 1 p.

10. Betlehem, József ; **Varga, Csaba** ; Berényi, Tamás ; Oláh, András

A hazai sürgősségi ellátás szakdolgozói humánerőforrás ellátottsága [The national

human resource supply in the emergency care]

NÉPEGÉSZSÉGÜGY 93 : 1 pp. 44-50. , 7 p. (2015)

11. Szabó, Barna ; **Varga, Csaba** ; Szelestei, Tamás

Acute renal failure caused by metformin intoxication

HYPERTONIA ÉS NEPHROLOGIA 19 : Suppl. 4 pp. 49-49. , 1 p. (2015)

12. **Varga, Csaba** ; Soós, Viktor ; Oláh, Tibor

Mérgezések, addikciók, tendenciák multidiszciplináris sürgősségi osztályon

In: Felvinczi, Katalin; Eisinger, Andrea; Demetrovics, Zsolt A Magyar Addiktológiai

Társaság X. Országos Kongresszusa : előadáskivonatok. Magyar Addiktológiai Társaság,

(2015) pp. 63-63. , 1 p.

13. **Varga, Csaba** ; Soós, Viktor ; Oláh, Tibor

Mérgezések, addikciók, tendenciák multidiszciplináris sürgősségi osztályon

ADDIKTOLÓGIA: ADDICTOLOGIA HUNGARICA 14 : Suppl. pp. 63-63. , 1 p. (2015)

14. **Varga, Csaba** ; Soós, Viktor ; Kovács, Mária

Multidiszciplináris sürgősségi osztályon megjelenő betegek epidemiológiai adatainak elemzése [Epidemiological analyses of the patients admitted to a multidisciplinary emergency department]

In: Betlehem, József; Radnai, Balázs; Deutsch, Krisztina; Bánfai, Bálint; Füge, Kata; Pék, Emese X. Pécsi Sürgősségi Napok / X. Critical Care Days in Pécs : Előadáskivonatok / Abstracts. Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2015) pp. 45-46. , 2 p.

15. **Varga, Csaba**

Kik az optimális sürgősségi ellátók hazánkban?

In: Betlehem, József; Radnai, Balázs; Deutsch, Krisztina; Bánfai, Bálint; Füge, Kata; Pék, Emese X. Pécsi Sürgősségi Napok / X. Critical Care Days in Pécs : Előadáskivonatok / Abstracts. Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2015) p. 13

16. Bánfai, B ; Fehér, K ; **Varga, Cs** ; Nagy, G ; Betlehem, J ; Marton, J ; Pék, E ; Deutsch, K; Radnai, B

Pre-hospital diagnosis of cerebrovascular events

CEREBROVASCULAR DISEASES 37 : Suppl 1 pp. 706-706. , 1 p. (2014)

17. Bánfai, B ; Drubits, K ; Nagy, G ; **Varga, Cs** ; Betlehem, J ; Marton, J ; Pék, E ; Deutsch, K ; Radnai, B

The effectiveness of CT scan in case of dizziness

CEREBROVASCULAR DISEASES 37 : Suppl 1 pp. 705-705. , 1 p. (2014)

18. Sárkány, Adrienn ; **Varga, Csaba** ; Szőts, Mónika ; Nagy, Ferenc

Basillar migraine as a rare cause of unconsciousness

In: "New era of emergency medicine: Old world new practice" International Conference on Emergency Medicine (ICEM) 2014. Programme. Hong Kong, Kína (2014) pp. 248-248. , 1 p.

19. **Varga, Csaba**

A kórházi sürgősségi ellátás helyzete az OSTK Tagozat szemszögéből,

34 p. (2014)

20. Várnai, Lilla ; Németh, Zsuzsanna ; Molnár, Adrienn ; Szvitán, Gábor ; Balogh, Orsolya ;
Varga, Csaba

A pulmonális embóliák ellátási stratégiája a Somogy Megyei Kaposi Mór Oktató

Kórház Sürgősségi Betegellátó Centrumában a PEITHO study tükrében

In: Lelovics, Zsuzsanna; Hunyady, Béla; Oláh, Tibor 52. Somogyi Egészségügyi Napok
programfüzete, előadásainak és posztereinek összefoglalói. Kaposvár, Magyarország :
Somogy Megyei Kaposi Mór Oktató Kórház, (2014) pp. 84-85. , 2 p.

21. Drubits, K ; Marton, J ; **Varga, Cs**

Szédülések elemzése a sürgősségi ellátásban, különös tekintettel a CT vizsgálat

jelentőségére

In: Betlehem, József; Radnai, Balázs; Marton, József; Deutsch, Krisztina; Pék, Emese; Bánfai,
Bálint 8. Pécsi sürgősségi napok. Előadáskivonatok – Abstracts. Pécs, Magyarország : Pécsi
Tudományegyetem Egészségtudományi Kar (PTE ETK), (2013) pp. 24-24. , 1 p.

22. Füredi, Gábor ; Bamberger, Éva ; Hetzman, T László ; **Varga, Csaba**

Túl a 100-on, avagy a kaposvári heliport 1 éve.

In: [Rudas, László] 12. Magyar sürgősségi orvostani kongresszus. MSOTKE – MOT közös
tudományos rendezvénye : Program és összefoglalók. Budapest, Magyarország : K&M
Congress, (2013) pp. 37-37. , 1 p.

23. Möbius, David ; Schrooten, Jochen ; Defillet, Tom ; Hughes, Karen ; Hardcastle,
Katherine ; Bellis, Mark ; Voorham, Lotte ; van Hasselt, Ninette ; Felvinczi, Katalin ; **Varga,
Csaba**; Demetrovic, Zsolt et al.

eSMIRTes final report. Electronic screening, brief intervention and referral to

treatment for (poly) drug users in emergency services , 94 p. (2013)

Megjelenés: Belgium.

24. Nagy, Tünde ; Sárkány, Adrienn ; Balogh, Gábor ; **Varga, Csaba** ; Oláh, Tibor

Mediastinitis, avagy mi rejlik a mellkasi panaszok hátterében?

In: [Rudas, László] 12. Magyar sürgősségi orvostani kongresszus. MSOTKE – MOT közös
tudományos rendezvénye : Program és összefoglalók. Budapest, Magyarország : K&M
Congress, (2013) pp. 33-34. , 2 p.

25. Sárkány, Adrienn ; Papp, Előd ; Tóth, Levente ; Kerkovits, Gábor ; Gaál, Ildikó ; **Varga, Csaba**

Benignus eltérés egy malignus ritmuszavar hátterében

In: [Rudas, László] 12. Magyar sürgősségi orvostani kongresszus. MSOTKE – MOT közös tudományos rendezvénye : Program és összefoglalók. Budapest, Magyarország : K&M Congress, (2013) pp. 34-34. , 1 p.

26. Sárkány, Adrienn ; Szőts, Mónika ; **Varga, Csaba** ; Nagy, Ferenc

Basillaris migraine, avagy még mi állhat az eszméletlen állapot hátterében.

In: [Rudas, László] 12. Magyar sürgősségi orvostani kongresszus. MSOTKE – MOT közös tudományos rendezvénye : Program és összefoglalók. Budapest, Magyarország : K&M Congress, (2013) pp. 32-33. , 2 p.

27. Szűcs, Orsolya ; Élö, Gábor ; Szabó, Léna ; **Varga, Csaba** ; Gál, János ; Zubek, László

Different aspects of therapy limitation: a comparative study of the nurse's view.

CRITICAL CARE 17 : Suppl. 2. p. S194 Paper: P527 , 1 p. (2013)

28. **Varga, Csaba** ; Kiss, Mariann

Gyermeksürgősségi ellátás a kaposvári Sürgősségi Betegellátó Centrumban.

In: [Magyar, Gyermekorvosok Társasága] Magyar Gyermekorvosok Társasága 2013. évi nagygyűlése. Programfüzet. Absztraktok. Budapest, Magyarország (2013) pp. 73-74. , 2 p.

29. **Varga, Csaba** ; Soós, Viktor

A súlyos sérülések ellátásához szükséges szakmai feltételek.

In: Betlehem, József; Radnai, Balázs; Marton, József; Deutsch, Krisztina; Pék, Emese; Bánfai, Bálint 8. Pécsi sürgősségi napok. Előadáskivonatok – Abstracts. Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2013) pp. 24-24. , 1 p.

30. **Varga, Csaba** ; Nagy, Ferenc ; Drubits, Katalin ; Heizler, György ; Lelovics, Zsuzsanna

A szédülés népegészségügyi jelentősége.

NÉPEGÉSZSÉGÜGY 91 : 3 pp. 169-169. , 1 p. (2013)

31. Bamberger, Éva ; Mészáros, Zoltán ; Simonics, Zsolt ; Füredi, Gábor ; Veress, Gábor ;

Varga, Csaba

Komorbiditás és ritka szövődmények kapcsolata a sürgősségi betegellátásban

In: [MSOTKE, – MOT] 11. Magyar Sürgősségi Orvostani Kongresszus. MSOTKE – MOT

közös tudományos rendezvénye. Program és összefoglalók (2012) pp. 30-31. , 2 p.

32. Beszterczán, Péter ; Papp, Előd ; Szász, Krisztina ; Völgyi, Zoltán ; Alotti, Nasri ; Lemle,

Zoltán ; **Varga, Csaba**

Komorbiditás a sürgősségi osztályon: aorta dissectió műtéti megoldása, korábban

ovarium tumor miatt kezelt betegnél.

In: [MSOTKE, – MOT] 11. Magyar Sürgősségi Orvostani Kongresszus. MSOTKE – MOT

közös tudományos rendezvénye. Program és összefoglalók (2012) pp. 31-32. , 2 p.

33. **Varga, Csaba**

A szédülések epidemiológiája – új adatok.

In: Deé, Kitti; Lelovics, Zsuzsanna A Somogy Megyei Kaposi Mór Oktató Kórház által

szervezett akkreditált továbbképzések programjai és válogatott összefoglalói, 2012 Kaposvár,

Magyarország : Somogy Megyei Kaposi Mór Oktató Kórház, (2012) pp. 23-24. , 2 p.

34. **Varga, Csaba**

A sürgősségi ellátás humánerőforrás szükséglete hazánkban [The needs of human

resource in emergency medical care in Hungary].

In: Betlehem, József; Radnai, Balázs; Marton, József; Deutsch, Krisztina; Pék, Emese 7. Pécsi

Sürgősségi Napok előadáskivonatok = 7th Critical Care Days in Pécs. Abstracts. Pécs,

Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2012) pp. 9-

9. , 1 p.

34. **Varga, Csaba** ; Nagy, Ferenc ; Drubics, Katalin ; Varga-Győrfi, Krisztina ; Papp, Zília ;

Lelovics, Zsuzsanna ; Oláh, Tibor

Is dizziness always covering a serious illness?

NEUROEPIDEMIOLOGY 39 : 3–4 pp. 248-248. , 1 p. (2012)

35. **Varga, Csaba**

S100B haszna a sürgősségi ellátásban

In: INDIA – Intenzív Diagnosztika Fórum. Magyar Aneszteziológiai és Intenzív Terápiás Társaság (MAITT) Tudományos Ülése programok és diasorok. Budapest, Magyarország (2012) pp. 35-40. Paper: 33 , 6 p.

36. Zubek, László ; Élő, Gábor ; Szabó, Léna ; Szűcs, Orsolya ; **Varga, Csaba** ; Gál, János

Different point of view in therapy restriction. Comparison of the opinions of Hungarian intensive care nurses and physicians.

INTENSIVE CARE MEDICINE 38 : Suppl. 1. pp. S176-S176. Paper: 0636 (2012)

37. Eredics, Péter ; Mészáros, Tamás ; **Varga, Csaba** ; Strausz, György

A HUMEDA orvosi döntéstámogató és oktató webrendszer

In: Networkshop 2011 : Kaposvár, [2011]. ápri lis 27-29.

Budapest, Magyarország : Nemzeti Információs Infrastruktúra Fejlesztési Intézet (NIIFI), (2011) pp. 1-36. Paper: HUMEDA, 36 p.

38. Gaál, Ildikó ; Kálmán, Zsolt ; Sárkány, Adrienn ; **Varga, Csaba**

Komorbiditások a Sürgősségi Osztályon, avagy az ismeretlen koponyaűri daganatok

In: 10. Magyar Sürgősségi Orvostani Kongresszus program és összefoglalók (2011) pp. 16-16. , 1 p.

39. Hartmann, Eszter ; Ködbaum, Zsanett ; **Varga, Csaba** ; Lelovics, Zsuzsanna ; Máté, Ágnes

Elhízott betegek a sürgősségi betegellátásban.

CARDIOMETABOLICA HUNGARICA 4 : Suppl. 2 pp. 42-42. , 1 p. (2011)

40. Kálmán, Zsolt ; Szappanos, Klára ; Gaál, Ildikó ; Szörényiné, Ványi Gabriella ; **Varga, Csaba**

Az erdő veszélyei

In: Hunyady, Béla; Lelovics, Zsuzsanna 51. Somogyi Egészségügyi Napok - Pannon Egészségügyi Napok: Előadások és poszterek összefoglalói. Kaposvár, Magyarország : Kaposi Mór Oktató Kórház, (2011) pp. 22-22. , 1 p.

41. Ködbaum, Zsanett ; Tolnai, Bianka ; Lelovics, Zsuzsanna ; Máté, Ágnes ; **Varga, Csaba**

Emergency care of the obese and extremely obese (prehospital and hospital) through the eye of the medical team

INTENSIVE CARE MEDICINE 37 : Suppl. 1 pp. S69-S69. (2011)

42. Lelovics, Zsuzsanna ; **Varga, Csaba**

Szédülés és elesés következtében fellépő sérülések gyakorisága

In: Nagy, Ferenc; Lelovics, Zsuzsanna „A szédülések diagnosztikája és kezelése" továbbképzés (Kaposvár, 2011. március 4–5.) előadások összefoglalói. Kaposvár, Magyarország : Kaposi Mór Oktató Kórház, (2011) pp. 8-8. , 1 p.

43. Muskát, Judit ; Máté, Ágnes ; Lelovics, Zsuzsanna ; **Varga, Csaba**

A cukorbetegek perioperatív menedzsmentje

In: Lelovics, Zsuzsanna; Vági, Zsolt A cukorbetegek kezelésének legújabb eredményei : Oktatási anyag : Kreditpontos távoktatás orvosoknak és gyógyszerészeknek. Dunakeszi, Magyarország : Euro Medica, (2011) pp. 51-58. , 8 p.

44. Szakáll, Aliz ; Molnár, Zsolt ; Csupor, Klára ; **Varga, Csaba** ; Oláh, Tibor

A has tengeralattjárója

In: Hunyady, Béla; Lelovics, Zsuzsanna 51. Somogyi Egészségügyi Napok - Pannon Egészségügyi Napok: Előadások és poszterek összefoglalói. Kaposvár, Magyarország : Kaposi Mór Oktató Kórház, (2011) pp. 41-41. , 1 p.

45. Tóth, Éva ; Beszterczán, Péter ; Jámbor, Anett ; Marosi, Ildikó ; **Varga, Csaba**

Gyilkos-e a gyilkos galóca?

In: Hunyady, Béla; Lelovics, Zsuzsanna 51. Somogyi Egészségügyi Napok - Pannon Egészségügyi Napok: Előadások és poszterek összefoglalói. Kaposvár, Magyarország : Kaposi Mór Oktató Kórház, (2011) pp. 44-44. , 1 p.

46. **Varga, Csaba**

Sürgősségi ellátási koncepciók hazánkban [Emergency medical care concepts in Hungary]

In: Betlehem, József; Radnai, Balázs; Marton-Simora, József; Deutsch, Krisztina; Pék, Emese VI. Pécsi Sürgősségi Napok előadáskivonatok = Abstracts of 6th Critical Care Days in Pécs. Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2011) pp. 8-8. , 1 p.

47. **Varga, Csaba**

Szédülések epidemiológiája

In: Nagy, Ferenc; Lelovics, Zsuzsanna „A szédülések diagnosztikája és kezelése" továbbképzés (Kaposvár, 2011. március 4–5.) előadások összefoglalói. Kaposvár, Magyarország : Kaposi Mór Oktató Kórház, (2011) pp. 7-7. , 1 p.

48. **Varga, Csaba** ; Ködbaum, Zsanett ; Tolnai, Bianka ; Máté, Ágnes ; Lelovics, Zsuzsanna

Attendance of obese (obese, extremely obese, morbid obese) patients by the ITLS protocol

INTENSIVE CARE MEDICINE 37 : Suppl. 1 pp. S235-S235. (2011)

49. **Varga, Csaba** ; Tóth, Levente ; Szőts, Mónika ; Nagy, Ferenc ; Oláh, Tibor

Komorbiditások koponyaűri lízisek kapcsán

In: Hunyady, Béla; Lelovics, Zsuzsanna 51. Somogyi Egészségügyi Napok - Pannon Egészségügyi Napok: Előadások és poszterek összefoglalói. Kaposvár, Magyarország : Kaposi Mór Oktató Kórház, (2011) pp. 46-46. , 1 p.

50. **Varga, Csaba**

Új kihívás a radiológiában „a sürgősségi betegellátás"

MAGYAR RADIOLÓGIA 84 : 2 pp. 115-115. , 1 p. (2010)

51. **Varga, Csaba**

Hirtelen halál – mit tegyen az orvos, mit tegyen a laikus

In: Rostás, László; Tenczer, József - A szív hullámhosszán. 1994–2009. Mosdós : „Aktuális kérdések a pulmonológiában és a kardiológiában" továbbképzés. Budapest, Magyarország : Magyar Kardiológusok Társasága Aritmia és Pacemaker Munkacsoportja, (2009) pp. 45-45. , 1 p.

52. **Varga, Csaba** ; Beszterczán, Péter ; Horváth, Gyula ; Orbán, Sándorné ; Keller, Éva

Az S-100 protein mérések alkalmazási lehetősége a sürgősségi ellátásban

In: 7. Magyar Sürgősségi Orvostani Kongresszus program és összefoglalók. (2008) pp. 26-27. Paper: O.13 , 2 p.

53. Egyed, Miklós ; Zádori, Péter ; Rajnics, Péter ; **Varga, Csaba** ; Horváth, Anita ; Horváth, Gyula

New pulmonary embolism diagnostic algorythm and the thromboprophylaxis in a Hungarian teaching hospital

BLOOD 110 : 11 pp. 68B-68B. Paper: 4000 , 1 p. (2007)

54. Horváth, Zoltán ; Imre, László ; Szentágotai, Attila ; Huszár, Péter ; Szász, Krisztina ; Horváth, Gyula ; Lakos, Lilla ; Szörényi, Péter ; Kiss, István ; **Varga, Csaba**; Hajdár, Csilla et al.

A haemorrhagiás stroke acut kezelése

In: 47. Somogyi Egészségügyi Napok programfüzet, programok és összefoglalók. Siófok, Magyarország : Siófok Város Kórház, (2005) pp. 28-29. Paper: 35 , 2 p.

55. Nyilas, Pál ; Prievara, Ferenc Tibor ; **Varga, Csaba**

A sürgősségi ellátás helyzete a Szülészeti Osztályon

In: 47. Somogyi Egészségügyi Napok programfüzet, programok és összefoglalók. Siófok, Magyarország : Siófok Város Kórház, (2005) pp. 28-28. Paper: 33 , 1 p.

56. **Varga, Csaba** ; Repa, Imre ; Soós, Viktor

Új sürgősségi osztály indult

In: Magyar Sürgősségi Orvostani Kongresszus 2005 program és összefoglalók. Budapest, Magyarország : K&M Congress, (2005) pp. 30-30. Paper: 29 , 1 p.

57. **Varga, Csaba** ; Szappanos, Klára ; Horváth, Gyula ; Balogh, Gábor

A tisztázatlan etológiájú haemothoraxról

In: Magyar Sürgősségi Orvostani Kongresszus 2005 program és összefoglalók. Budapest, Magyarország : K&M Congress, (2005) p. 29 Paper: Sz. 28

58. **Varga, Csaba** ; Szappanos, Klára ; Balogh, Gábor ; Horváth, Gyula ; Ballér, Csaba

A tisztázatlan etiológiájú haemothoraxról

In: 47. Somogyi Egészségügyi Napok programfüzet, programok és összefoglalók. Siófok, Magyarország : Siófok Város Kórház, (2005) pp. 59-59. Paper: 162 , 1 p.

59. **Varga, Csaba**

A sürgősségi ellátásban eltöltött egy év tapasztalata

In: 47. Somogyi Egészségügyi Napok programfüzet, programok és összefoglalók. Siófok, Magyarország : Siófok Város Kórház, (2005) pp. 29-29. Paper: 37 , 1 p.

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Diagnostic Challenges in the Emergency Setting

című doktori értekezésemet a mai napon benyújtom a(z)

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Egyúttal nyilatkozom, hogy jelen eljárás során benyújtott doktori értekezésemet

- korábban más doktori iskolába (sem hazai, sem külföldi egyetemen) nem nyújtottam be,

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- az elmúlt két esztendőben nem volt sikertelen doktori eljárásom,

- öt éven belül doktori fokozatom visszavonására nem került sor,

- értekezésem önálló munka, más szellemi alkotását sajátomként nem mutattam be, az irodalmi hivatkozások egyértelműek és teljesek, az értekezés elkészítésénél hamis vagy hamisított adatokat nem használtam.

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