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The change of the effectiveness of acute care due to integrative education

Diagnostic Challenges in the Emergency Setting

Doctoral (Ph.D.) thesis

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1 Introduction

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 set up a timely diagnose and initiate treatment encompassing a wide range of diseases involving critical thinking and be knowledgeable in various areas of the medical field.

This thesis includes two important studies. Both demonstrate the difficulties inherent in Emergency Care. In periarrest situations and during resuscitation it is essential to rule out reversible causes, including hyperkalemia, which is a relatively common condition and may lead to fatal cardiac arrhythmias. The ECG signs of hyperkalemia, such as peaked T waves, AV blocks, widening of the QRS and ventricular fibrillation have already been documented. The goal of our study was to compare the prevalence of ECG alterations suggestive of hyperkalemia in normokalemic and hyperkalemic patients. 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.

Case reports within medicine are important because they describe the special aspects and treatment options of certain medical conditions. Therefore, we found it important to describe the rare case of a snake envenoming by the *Vipera berus bosniensis*. In Europe there are three species of venomous snakes categorized as medically important, from which *Vipera berus* is the most widespread species. Envenomations mostly cause local symptoms, but have been associated with causing systemic symptoms, such as hypotension, gastrointestinal and coagulation disorders and neurotoxicity as well. The aim of our case presentation was to describe the course of the illness and its treatment and so to expand the knowledge about *V. b. bosniensis* envenomings.

2 Aims

Taken together, the goals of my studies were to determine the following:

2.1 Regarding the study on ECG alterations in normokalemic vs hyperkalemic patients:

1. Are there any differences between the baseline characteristics 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 and 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 in normokalemic versus hyperkalemic patients?
5. Is the ECG a suitable tool in the diagnosis of hyperkalemia in the prehospital, emergency setting?

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

6. 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?
7. Which unique clinical signs of snakebite neurotoxicity could be observed in our patient following *Vipera berus bosniensis* envenoming?
8. Do the neurotoxic components of *Vipera berus bosniensis* cause a disturbance in the neuromuscular junctions?
If so, how can this disturbance be objectively observed?
9. What is the possible explanation for the slowly evolving and prolonged neurological manifestations observed in our patient following the snakebite?
10. What are the clinical implications of our case report in the treatment of snakebites at the Emergency Department?

3 Materials and Methods

3.1 Regarding the study on ECG alterations in normokalemic and hyperkalemic patients

3.1.1 Study design. Patients.

Electrocardiograms and data from 135 hyperkalemic (moderate (6,0-7,0 mmol/L) hyperkalemia n=97; severe (>7,0 mmol/L) hyperkalemia n=38) and 170 normokalemic (3,4-5,1mmol/l) patients were analyzed using the Hospital's database. All patients were over 18 years of age and were required to have had an ECG performed within one hour of the laboratory draw.

3.1.2 ECG analysis

The ECG curves of each patient were analyzed by two board-certified emergency physicians, independently.

3.1.3 Statistics

Data was analysed using SPSS22 software. P values ≤ 0.05 were considered to be statistically significant.

4 Results

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

Patient characteristics

Patients in the hyperkalemic group were older than patients in the normokalemic (control) group. A significantly higher percentage of hyperkalemic patients took medication that may elevate potassium levels, than normokalemic patients. Comorbidities were also significantly more prevalent in hyperkalemic patients. (*Table 1.*)

	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
Spirolactone	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 1: 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, (*: $p \leq 0,05$)

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

In the control group, 24.0% of normokalemic patients had ECG alterations suggestive of hyperkalemia and from these. 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 at all. (Table 2, Figure 1)

		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
		I ECG alteration	≥2 ECG alterations									
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 2: Frequency of ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic (moderate and/or severe) patients (*: $p \leq 0,05$), Cardiac arrest included asystole, ventricular fibrillation, pulseless ventricular tachycardia and pulseless electric activity.

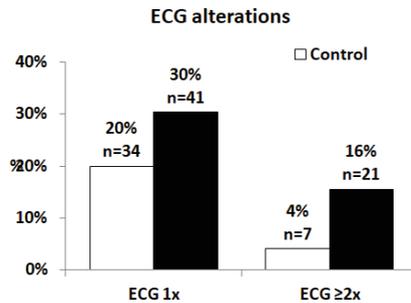


Figure 1: The frequency of single and multiple ECG alterations suggestive of hyperkalemia in normokalemic and hyperkalemic patients

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). (Table 2, Figure 2.) Wide QRS (18.5%) was the only ECG alteration significantly more frequent in all hyperkalemic patients compared to normokalemic patients (8.2%). (Table 2, Figure 2) Cardiac arrest occurred in 8 patients with hyperkalemia (Table 2).

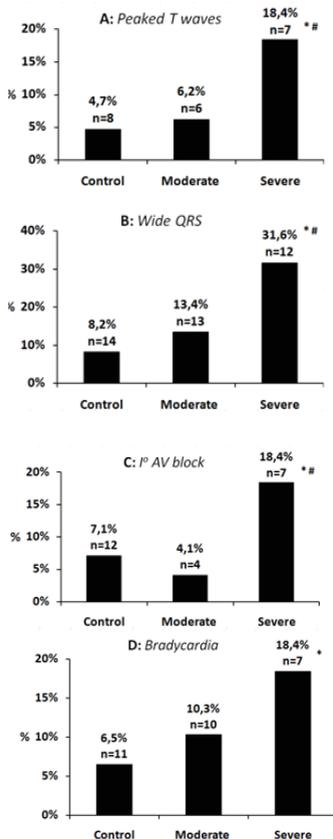


Figure 2: The frequency of ECG alterations suggestive of hyperkalemia in normokalemic, moderately hyperkalemic and severely hyperkalemic patients (*: $p < 0,05$ vs control, #: $p < 0,05$ vs moderate hyperkalemia) A: Peaked T waves; B: Wide QRS; C: Ist degree AV block; D: Bradycardia

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

Atrial fibrillation was significantly more frequent in severely hyperkalemic patients (26,3%) compared to normokalemic patients (10,6%). 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 3, Figure 3).

		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 3: The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients. (: p≤0,05)*

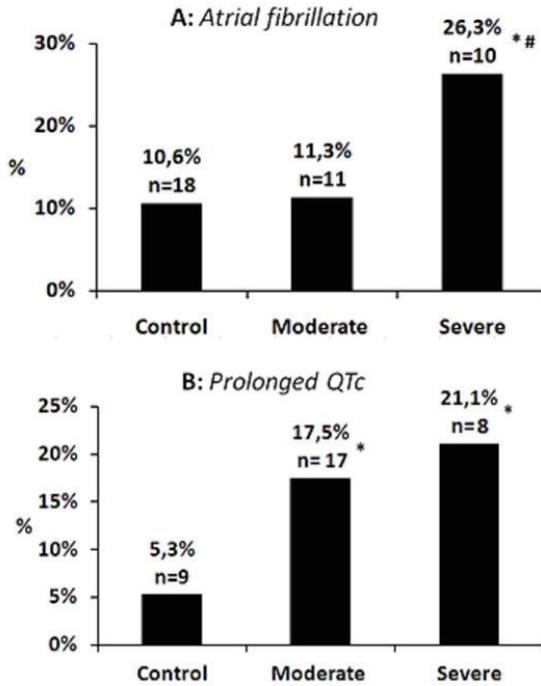


Figure 3: The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients

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

Case report

A 63-year-old man was bitten on his left index finger by a uniformly black adder in Kaszó, Somogy County, South-Western Hungary on **May 04th**, 2017. He was transported by ambulance to the Hopsital. He experienced sweating and nausea combined with a stomach ache. A small local haematoma and minimal local swelling were visible around the fang marks. The patient complained of nausea and dizziness and vomited. An ECG showed horizontal ST depression in leads V5-6. Tenderness of the abdomen and slightly elevated blood pressure of 160/100 mmHg were recorded a little later on, then, the patient developed intense abdominal colic and profuse diarrhoea. Antivenom (500 IU i.m. Viper Venom Antitoxin®, Biomed, Warsaw) and supportive therapy: chloropyramine (20 mg i.v.), and methylprednisolone (125 mg i.v.) were given. The next morning (**05th May**) the patient was unable to open his eyes and he reported constant double vision. The pupils were equal in size and moderately dilated, the pupillary light reflexes were intact. Complete bilateral ptosis with external ophthalmoplegia was diagnosed (Figure 4).

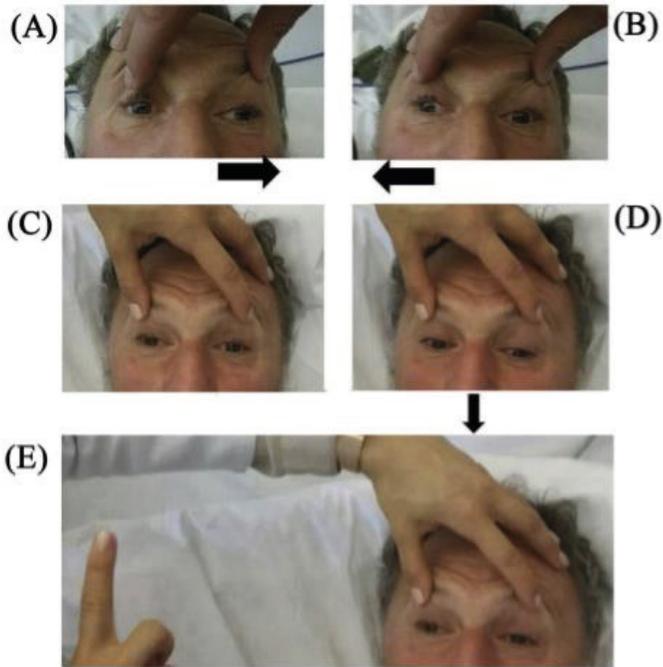


Figure 4: Complete bilateral ptosis and ataxic nystagmus in the patient. (A): Gaze to right, abducted right eye shows paralysis of left medial rectus. (B): Gaze to left, abducted left eye shows paralysis of right medial rectus. (C) and (D): The eyeballs diverged both horizontally and vertically while 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.)

Single-fiber electromyography (SfEMG) was performed following neurological consultation. The patient received neostigmine-methylsulfate (0,5 mg i.v.) in infusion and an atropine-sulfate (0,5 mg i.m.) injection.

On the **06th of May**, the patient felt weak and still had ptosis but he was already able to open his eyelids to uncover the pupils. Two days later, the ptosis and the the paralysis of the extraocular muscles almost completely resolved.

6 Discussion

6.1 Discussion related to the study on: “ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients”

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.

ECGs have often been shown to be normal in hyperkalemia and Wrenn et al. concluded that even in high-risk patients, the ECG was not a sensitive method of detecting hyperkalemia. In accordance with these investigations, we found that less than half of the hyperkalemic patients exhibited ECG changes suggestive of hyperkalemia. A surprisingly high proportion (24%) of normokalemic patients exhibited ECG alterations suggestive of hyperkalemia.

According to the results of the prospective population-based Rotterdam study, participants with hypokalemia had a higher risk of atrial fibrillation. Our results showed, however, that atrial fibrillation was more prevalent in severely hyperkalemic patients compared to normokalemic patients. We attributed these results to the synergistic effect of two groups of diseases, chronic kidney disease and heart failure, often present in patients with high potassium levels. Our results also imply that prolonged QTc and atrial fibrillation could also draw attention to hyperkalemia, besides the more acknowledged ECG manifestations of hyperkalemia.

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. In keeping with these earlier reports, we found that the application of these types of drugs was also more common in patients with elevated potassium levels.

Our findings imply that the ECG is not a reliable tool in the diagnosis of hyperkalemia and that treatment of hyperkalemia may not be prudent prior to laboratory-confirmation. 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.

6.2 Discussion related to the “Case report of *Vipera berus 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.

The immediate local burning pain experienced by the patient as well as the minimal hematoma were consistent with the local symptoms reported in previous cases of envenomings. Nausea, vomiting and diarrhoea develop frequently in *V. berus* envenomings as in our patient’s case.

Venom of *V. b. berus* is considered potentially cardiotoxic and cardiac complications are often. 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 *Vipera berus. bosniensis*. Peripheral neurotoxicity is a typical neurological manifestation. Envenomed patients may also show ataxic nystagmus in lateral directions. This unique clinical sign of snakebite neurotoxicity combined with complete extraocular muscle palsy, was observed in our case.

If the snake’s venom contains prejunctional neurotoxic PLA2s, the neuromuscular paralysis develops slowly and takes longer to recover. In the case of our patient, neostigmine was applied the day following the bite in an attempt to ameliorate the neurological signs and symptoms. The slowly evolving and prolonged neurologic manifestations as well as the lack of benefit from the antivenom and neostigmine therapy, strongly suggest that the venom of the South-Western Hungarian *Vipera berus bosniensis* in our patient’s case contained prejunctional neurotoxic PLA2(s).

7 Conclusions

Summary of the results

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). A significantly higher percentage of hyperkalemic patients took medication that may increase potassium levels, than normokalemic patients.
2. 24% of normokalemic patients and only 46% of patients with moderate or severe hyperkalemia had ECG alterations suggestive of hyperkalemia.
3. Significantly more patients with severe hyperkalemia had wide QRS, bradycardia, peaked T-waves and 1st degree AV block compared to normokalemic patients. 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. 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 occurrence of heart failure and associated drug treatment may be responsible for our observations.
5. 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. .
6. The observed mild local symptoms at the site of the bite were characteristic of *Vipera berus bosniensis* envenoming. The prolonged and marked systemic (gastrointestinal, cardiotoxic and neurotoxic) symptoms can also be characteristic of moderate and severe envenomings caused by this *Vipera* ssp.

7. Following the snakebite, the patient developed neurotoxic symptoms. The frequently occurring complete extraocular ophthalmoplegia and the extremely rare ataxic nystagmus could also be observed, which latter symptom has not yet been published in cases of European snake bites.
8. sfEMG showed 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 blockade.
9. We hypothesized that the observed neuromuscular blockade was due to the prejunctional PLA2 (s) present in the venom of South-Western Hungarian adders.
10. 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, healthcare professionals should be prepared for the treatment of moderate to severe systemic symptoms in patients following South-Western Hungarian adder envenomings. The choice of antivenom therapy should also be carefully considered. 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.

8 Publications

8.1 Publications related to the thesis

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

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 Other publications

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) Folyóíratcikk)

IF: 0.252

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

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)

Radnai, Péter; Szóts, Mónika; Rádai, Ferenc; Horváth, Gyula; **Varga, Csaba**; Fogas, János; Szörényi, Péter; Horváth, Zoltán; Bajzik, Gábor; Moizs, Mariann et al.

Az akut ischaemiás stroke neurointervenciók 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

Varga, Csaba; Nagy, Ferenc; Drubits, Katalin; Lelovics, Zsuzsanna; Varga, Györfi 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

Varga, Csaba; Orbán, Sándorné; Lelovics, Zsuzsanna; Zádori, Péter; Bethlehem, 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)

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

Cumulative IF: 5.078

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