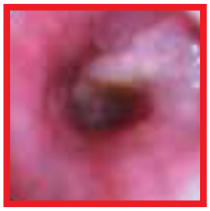
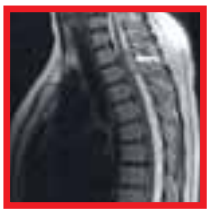
SCRIPTA MEDICA 42

Časopis Društva doktora medicine Republike Srpske
Journal of the Medical Society of the Republic of Srpska

Godina: 42. • Broj 1 • maj 2011.
Časopis Društva doktora medicine Republike Srpske

Vol. 42 • No 1 • May 2011.
Medical Society of the Republic of Srpska





www.scriptamedica.com

Scripta Medica (Banja Luka)

Časopis Društva doktora medicine Republike Srpske

ISSN 0350-8218

Tiraž: 1.000 primjeraka

Sadržaj

Contents

EDITORIAL

Progress in the Prevention of Stroke

The Questions and Answers section presents the use of recently developed oral anticoagulants[1]. Because introduction of these drugs offers one of the most significant innovations in clinical practice in the past sixty years,[2] we would call attention to the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study[3] that compares the effectiveness of dabigatran, a new oral anticoagulant, with warfarin for patients with atrial fibrillation (AF).

Vitamin K antagonists, such as warfarin, protect against stroke in patients with AF. However, vitamin K antagonists can produce variable anticoagulant responses because of genetic polymorphisms, dietary vitamin K intake, and alterations of their metabolism. Coagulation monitoring and frequent dose adjustments are thus necessary to ensure proper therapeutic level of anticoagulation. This is troublesome for patients and physicians and expensive for the health system. The new oral anticoagulants produce a steady anticoagulant effect when given in fixed doses.

The RE-LY study included more than 18.000 AF patients that received either dabigatran (150 mg twice daily or 110 mg twice daily) without coagulation monitoring or warfarin (titrated dose given on an open-label basis). Dabigatran (150 mg twice daily) was found to be superior to well-controlled warfarin. According to the manufacturers, the renal dosing for dabigatran should be adjusted according to the creatinin clearance (CrCl) as follows: for CrCl 15-30, the dosage is 75 mg twice daily; for CrCl<15 or hemodialysis, the dosage is not defined. Ischemic and hemorrhagic stroke rates were lower in patients treated with dabigatran than in patients treated with warfarin. The rates of disabling or fatal stroke were also lower in the dabigatran-treated group.

Dabigatran was approved in Europe and the USA under the name "Pradaxa." In addition to recommended indications, dabigatran is a potential alternative to warfarin in patients requiring cardioversion.[4] Additional oral anticoagulant treatments (apixaban, rivaroxaban, edoxaban) for stroke prevention in patients with AF are on the horizon, and we expect that the price of this treatment will soon become affordable. One possible advantage is that these pharmacological innovations can be substituted for expensive electrophysiological atrial ablations that are not available to everyone.

The prevalence of atrial fibrillation (AF) is 10- to 20-fold higher in patients with end-stage renal failure than in the general population. Risk factors for development of AF in patients with severe renal impairment include degenerative valvular heart disease, accelerated vascular nervous system activation, and modulation of the renin-angiotensin system.[5] The clinical benefit of oral anticoagulation therapy for primary and secondary prevention of stroke is based on studies that exclude AF patients with severe renal impairment due to major bleeding episodes in anticoagulated hemodialysis. New oral anticoagulants probably should not be contraindicated in such patient population, but rather be considered on a patient-by-patient basis.[6]

Antithrombotic drug choices for stroke prevention of the patients with AF include addition of antiplatelet agents (aspirin, and aspirin plus clopidogrel) or anticoagulants (warfarin and new anticoagulants). The choice of therapy depends on the estimated risk of thromboembolic events in AF. According the CHA_2DS_2-Vasc. Score, the risk score (given in brackets) considers the following factors: left ventricular dysfunction (1), hypertension (1), age >75 (2), diabetes (1), prior stroke or TIA (2). A total score of 0 does not require therapy, a score of 1 requires ASA or anticoagulation, and a score of 2 or above requires anticoagulation for prevention of AF.

It is worth mentioning that the American Heart Association accepted a new definition for transient ischemic attacks (TIA).[7] Previous definition of TIA presumed a focal neurological deficit of vascular origin lasting less than 24 hours. The new definition is not based on a time limit; instead, it is based on the absence of brain injury, and is described as "a transient episode of neurological dysfunction caused by brain, spinal cord or retinal ischemia without acute infarction." A patient with transient symptoms but evidence of acute infarction on imaging studies (such as diffusion-weighted MRI) is now considered to have had a stroke.

Scripta Medica

References

1. Đokanović N, Stojaković N, Tomić N. Questions and answers. *Scripta Medica* 2011;42:46-52.
2. Galanis T, Thomson L, Palladino M, et al. New oral anticoagulants. *J Thromb Thrombosis* 2011:31:310-20.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
4. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;123:131-6.
5. Mariunigh R, Lane DA, Lip GYH. Severe renal impairment and stroke prevention in atrial fibrillation. *JACC* 2011;57:1339-48.
6. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. *Chest* 2010;138:1093-10.
7. Albers GW. Stroke: more protection for patients with atrial fibrillation. *Lancet Neurol* 2010;9:2-4.

EDITORIAL

Scripta Medica introduces a new column: Letters to the Editor

This issue of *Scripta Medica* contains three letters to the Editor.[1-3] This new column provides space for comments, questions, opinions and criticism of the work published in the journal. Letters allow our readers to respond to articles, and we will try to publish responses of the authors within the same issue. Because the original authors have the last word, any responsive criticism should be well documented, so that the letter writer becomes part of an informative discussion.

A letter to the editor provides a means of communication between the author of an article and the reader, allowing a dialog about the subject to take place. Although it may not be original research *per se*, a letter may provide new insight, make corrections, offer alternate theories, or request clarification about content printed in the journal. By providing post-publication in print, published evidence may be strengthened or challenged by such commentary, thus further shaping our biomedical knowledge.

Generally, a letter to the editor will include comments for or against the information provided by a previous publication, communication of a brief case report, or concise communication of clinical or investigative data. A letter in response to an article should be courteous and interesting; it should contain specific and reasoned arguments rather than generalizations and emphasize only a few specific points.

We will also consider very brief communications that do not justify a full report; these will be published as letters. Such letters may include cases that give novel insight into pathogenesis, diagnosis, management or prevention of a disease. However, our journal imposes restrictions on the length and number of accompanying tables or figures of such submissions (see Instructions for Authors).

A concise report in the form of a letter needs to explain, briefly, the rationale and objectives of the study, and it should reference the methods used, include essential data obtained—preferably by tabulated results—and end with a final conclusion. [4] According to the International Committee of Medical Journal Editors[5] "authors of correspondence should be asked to declare any competing or conflicting interests." Such reports from the Authors of a letter should provide this information with the manuscript.

Resistance to criticism in medical research[6,7] should be gradually diluted and dialog encouraged. Institution of this column, Letters to the Editor, in the *Scripta Medica* is an important step towards this goal. Since letters are often the most frequently read parts of journals, we believe that *Letters* will be both entertaining and useful to our readers and authors.

Rajko Igić

References

1. Ivanović Z. Regenerative surgery may be soon a therapeutic revolution. Scr Med 2011;42,33.
2. Bašić-Panić B. Handicapped Persons: Medical Doctors. Scr Med 2011;42:33.
3. Pancholi N, Patel J. Fulminant burning mouth syndrome. Scr Med 2011;42:34.
4. Hall GM. How to write a paper, third edition. London, BMJ Books, 2003.
5. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submit-ted to biomedical journals. Available at: http://www.icmje.org. Accessibility verified on May 1st, 2011.
6. Horton R. Postpublication criticism and shaping of clinical knowledge. JAMA 2002;287:2843-7.
7. Petric B. Prikazi knjiga u Srpskom arhivu i Vojnosanitetskom pregledu: Istorijska perspektiva. Scripta Medica 2010;41:94-6.

ORIGINAL ARTICLE

Simvastatin improves survival and reduces leukocyte recruitment and hepatocyte apoptosis in endotoxin-induced liver injury

L. Nežić[1], Lj. Amidžić[2], V. Jaćević[3], S. Dobrić[3], R. Škrbić[1], M. P. Stojiljković[4], J. Komić[5], S. Stoisavljević-Šatara[1]

[1]Department of Pharmacology, Toxicology and Clinical Pharmacology, Medical Faculty, Banja Luka; [2]Department of Pathology, Clinical Center Banja Luka, Republic of Srpska, Bosnia and Herzegovina; [3]National Poison Control Centre, Medical Military Academy, Crnotravska 11, 11000 Belgrade, Serbia, [4]Department of Pharmacology, Medical Faculty, University of East Sarajevo, 51000 Foča, Republic of Srpska, Bosnia and Herzegovina; [5]Department of Statistics, Faculty of Economics, University of Banja Luka, Republic of Srpska, Bosnia and Herzegovina.

Correspondence
Lana Nežić, MD, MSc
Zavod za farmakologiju, toksikologiju i kliničku farmakologiju
Medicinski fakultet
Save Mrkalja 14
78000 Banja Luka
Republic of Srpska
Bosnia and Herzegovina
Phone: +387 51 214 117
E-mail: lanne@doctor.com

ABSTRAKT

Background. Endotoxemia provokes excessive host response to bacteria or microbial compounds, resulting in systemic inflammation, organ injury and mortality.
Aim: This study examined the effects of simvastatin on survival and liver injury in endotoxic shock in a rat model of endotoxemia.
Methods. Male Wistar rats were injected intraperitoneally with E.coli-lipopolysaccharide (LPS) and the medial lethal dose (LD_{50}) was determined. Simvastatin was given orally (5-40 mg/kg body weight) for five days prior to either a single LD_{50} dose of LPS or 2, 2.5 or 3x LD_{50}. Liver damage was assessed by histological examination and expressed as a tissue damaged score (TDS). Another group of rats was treated with simvastatin and then challenged with LPS to determine the degree of apoptosis in hepatocytes, liver immune cells, and cleaved caspase-3 activity after 24h of endotoxemia.
Results. Endotoxemia caused substantial mortality with assiciated leukocyte infiltration, liver injury (TDS = 3.67, SD = 0.55), as well as notable apoptosis of hepatocytes and resident liver macrophages. Simvastatin, in a dose-dependent manner significantly reduced LPS-induced mortality, hepatocellular damage (TDS = 1.5, SD = 0.55), inflammatory infiltration, and dte drug markedly decreased apoptosis and expression of cleaved caspase-3.
Conclusions. Simvastatin improves survival in endotoxic shock and prevents endotoxemic liver injury by inhibiting leukocyte infiltration and hepatocellular apoptosis. These results suggest that simvastatin could be used to prevent endotoxemia-associated liver dysfunction by simvastatin.

KEY WORDS
simvastatin, liver injury, endotoxin, inflammation, apoptosis

(Scr Med 2011;42:7-13)

Submitted: April 30, 2011
Accepted: May 26, 2011

Sepsis is a leading cause of death among critically ill patients. Despite extensive investigation over the past three decades, the incidence of sepsis and sepsis-related deaths is increasing.[1] Endotoxin or lipopolysaccharide (LPS), the dominant portion of the outer membrane of Gram-negative bacteria, activates the inflammatory cells and increases production of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α, and other factors, such as nitric oxide (NO).[2-4] Excessive production of pro-inflammatory mediators, by the host in response to LPS challenge results in systemic inflammation, tissue injury and organ failure, events that are strongly associated with septic shock.[5] The relative severity of sepsis depends upon the balance between pro-inflammatory and anti-inflammatory states. Liver failure is an insidious problem for critically ill patients. Numerous studies suggest that hepatic infiltration of leukocytes as a cause of endotoxemic liver damage.[6-7] The recruitment process of leukocytes in venules is a multistep process, involving adhesion of rolling leukocytes via a selectin-mediated mechanism,[8,9] although leukocyte trapping in hepatic sinusoids occurs without of this interaction.[10] Contact between the lymphocyte function antigen-1 (LFA-1) and a family members of adhesive molecules expressed on endothelial cells firmly establishes leukocyte adhesion in the liver microvascular endothelium in endotoxemic mice. [11] Transendothelial migration and tis-

sue accumulation of leukocytes in the liver depend upon the formation of chemokines in hepatocytes. Once established within the extravascular parenchyma, these accumulated leukocytes promote hepatocellular apoptosis, resulting ultimately in liver failure.

Statins, or 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have had a major impact on healthcare by decreasing cardiovascular events. The efficacy of statins has been attributed primarily to their lipid-lowering properties. However, a growing body of evidence highlights statin actions independent of its lipid-lowering properties.[12, 13] These include anti-inflammatory and antioxidant effects. As a result, recently issued, a guideline recommends that patients with diabetes and cardiovascular disease should initiate statin therapy regardless of baseline LDL cholesterol levels.[14] Retrospective and prospective observational studies indicate that that statin treatment reduces the incidence and mortality of sepsis, although not all investigators agree. [15] Prospective clinical trials are currently evaluating the safety and efficacy of statins in septic patients. Along with these observational studies in humans, [15] mouse models of sepsis and endotoxemia also indicate the protective actions of statins, which reportedly reduce mortality, preserve cardiac function, ameliorate inflammation and improve bacterial clearance.[5, 16] It is not yet known if these beneficial effects will obtain as well in endotoxemic liver injury.

We used a well-known rat model for endotoxemia to determine if oral simvastatin, could improve survival in endotoxic shock and prevent endotoxin-induced leukocyte recruitment, hepatocellular apoptosis and liver injury.

Materials and Methods

Animals. Experiments were performed on male Wistar rats, 6 - 8 weeks old (180 to 220 g body weight - b.w) bred at the Farm for Experimental Animals, Military Medical Academy, Belgrade, Serbia, and kept in the animal unit 7 days before the experiment. They were housed in plastic cages, under standard laboratory conditions (21 - 22°C, 12 h light/dark cycle, 30 - 70% relative humidity). They were supplied with commercial food and tap water *ad libitum*. The animals were deprived of food 18 – 20 h before beginning of experiments with free access to tap water. Experimental groups consisted of six animals each. The study protocol was based on the Guidelines for Animal Study no. 282-12/2002 (Ethics Committee of the Military Medical Academy, Belgrade, Serbia).

Pharmacological Interventions. Simvastatin (Krka, Novo Mesto, Slovenia) was dissolved in 0.5% methylcellulose (Sigma, Taufkirchen, Germany), as 10 or 20 mg/mL stocks. *Endotoxin* from *E. coli* serotype 0127:B8 (Sigma Aldrich, Germany) was injected intraperitoneally (i.p.) after dilution with sterile pyrogen-free physiologic saline solution, in a volume of 1 mL/kg.

Endotoxin-induced lethality in rats. The animals were divided into three groups (n=6 per group), given saline orally (p.o.) and challenged i.p with one of the three doses of LPS (10, 20, 30 mg/kg b.w.). The lethality and changes in body temperature were then monitored over the next 7 days. Mortality resulting from LPS was recorded and the median lethal dose (LD_{50}) of LPS i.p. was calculated.[17]

Protective effects of of simvastatin on mortality induced by lethal dose of endotoxin. To establish the effect of short-term pretreatment of simvastatin on the survival of rats injected with LD_{50} of LPS, the animals were divided into four groups (n=6 per group); simvastatin was given p.o. in one of the four doses (5, 10, 20 and 40 mg/kg b.w, respectively) per day for 5 days. One and a half h after the last dose of simvastatin the single LD_{50} of LPS was injected i.p. Control group was treated with saline for 5 days, before a single LD_{50} of LPS was injected. The rates of survival of animals and changes in body temperature were monitored for a period of 7 days.

The doses of simvastatin in our study were comparable to those that had previously been used in rat/murine studies *in vivo* (typically 10 - 100 mg/kg/day); however, they were higher than those used in humans because of a significant up-regulation (3- to 8-fold) of HMG-CoA reductase induced by statin treatment in rodents.[18] We also investigated protective efficacy of the drug on survival rates. Simvastatin (5 - 40 mg/kg) was administered p.o. for five days prior to a single absolute lethal dose of LPS (2x, 2.5x or 3x LD_{50} of LPS). The Litchfield&Wilcoxon procedure[17] was used to calculate LD_{50} dose of LPS in the simvastatin pretreated group.

The protection index (PI) was calculated as a ratio of LD_{50} of LPS in simvastatin pretreated group to LD_{50} of LPS. We calculated the effective dose (ED_{50}) of orally administered simvastatin by the same procedure.[17] The ED_{50} is defined as the amount of drug that produces a therapeutic response in 50% of treated subjects.

Histopathological examination. Tissue sections from rat livers were stained with haematoxylin and eosin (H&E). Random fields from each specimen were magnified 20x and viewed with an Olympus-2 microscope (Tokyo, Japan).

Semiquantitative analysis. The type, degree and severity of tissue lesions along with the number of inflammatory cells were assessed in tissue samples from each animal and they were counted in six separate visual fields under 40x magnification. The severity of liver lesions (tissue damage score or TDS) was determined according to a 5-point semi-quantitative scale based on the number of inflammatory cells, haemorrhages, edema, and the number of foci involved. Grade "0" indicated normal findings, while grade "5" indicated pronounced plasmolysis and cariolysis, along with massive hemorrhagic foci and polymorphonuclear cell (PMNC) infiltration.

Immunohistochemical determination of apoptosis-regulating Cleaved Caspase-3. Liver samples from control and treated groups were compared 24h after the animals were treated. The control group was treated with a single LD_{50} dose of LPS; the treatment group received simvastatin (20 mg/kg) for five days prior to administration of a single LD_{50} dose of LPS. Paraffin-embedded sections of liver tissue were stained with a polyclonal rabbit antibody to cleaved caspase-3 (Thermo Scientific Fischer Ab-4, RB 1197-R7, USA), according to the manufacturer's instructions. Diaminobenzidine tetrahydrochloride was used to develop the antigen-antibody complex, and all slides were counterstained with H&E, dehydrated, and mounted. Appropriate positive controls were processed in parallel. For each liver section, random visual fields (100x or 200x) were evaluated, and immunopositive cells were assessed for antibody staining (negative, weak, moderate, strong) as a reflection of caspase-3 expression. [19]

Statistical analysis. All data are reported as the mean ± standard deviation (SD), and groups were compared by non-parametric statistical tests (t-test, Mann-Withney, Kruskal–Wallis rank test). The median lethal dose of endotoxin (LD_{50} of LPS), the effective dose 50% (ED_{50}) of simvastatin and the protective index were calculated by the Lichfield and Wilcoxon procedure,[17] and 95% confidence intervals were derived. Differences with values of P<0.05 were considered significant.

Results

Determination of LD_{50} of LPS and protective dose of simvastatin. Table 1 shows that LPS increased lethality of rats in a dose-dependent manner. The LD_{50} of i.p. LPS was calculated to be 22.15 (95% CI 16.5-29.1) mg/kg.

40 mg/kg of simvastatin (p=0.04). All three doses of LPS induced significant hypothermia (<35, 5°) compared to baseline body temperature within 6 h after challenge (p<0, 05). These findings closely predicted lethality within the first 24 hours. Body temperature returned to normal after 24 hours in animals that survived. We did not observe significant changes in body temperature in rats treated with 20 and 40 mg/kg of simvastatin. Simvastatin alone had no effect on body temperature (data not shown).

Protection index and anti-inflammatory effective dose of simvastatin in endotoxic shock. We established the protective efficacy of orally administered 20 mg/kg simvastatin against lethal doses of LPS (2x, 2.5x, 3x LD_{50}). Simvastatin improved survival up to 67% (p<0,05) in animals treated with 2x LD_{50} of LPS (Table 2). We calculated that the LD_{50} of LPS increased significantly to 46, 34 (37, 86-56, 74) mg/kg in the simvastatin pretreatment group and determined that the PI = 2.09.

To test the protective effect of statin against a single lethal dose of LPS (2xLD_{50}), we pretreated animals with 5, 10, 20, 40 mg/kg of simvastatin. The highest dose (40 mg/kg) completely prevented mortality (Table 2), while survival obtained with 20 mg/kg of simvastatin was significantly less (p<0, 05) (Table 2). The ED_{50} was 14.14 (22, 41 - 8, 93) mg/kg.

Effects of simvastatin on liver histology in endotoxic shock. Since leukocyte recruitment is a rate-limiting step in endotoxin-induced liver injury, we analyzed hepatic leukocyte infiltration and liver architecture in the randomly selected liver sections. As seen in Figure 1B; a single dose of LD_{50} of LPS induced severe liver damage characterized

Table 1. Median lethal dose (LD50) of LPS and effect of simvastatin on mortality.

Simvastatin (mg/kg/day p.o.)[b]	LPS (mg/kg, i.p)[a]	No. of rats (dead/total)	LD_{50} of LPS (95% CI) (mg/kg i.p)
None	10	0/6	22.15 (16.5-29.1)
	20	3/6	
	30	4/6	
5	LD_{50}	3/6	-
10		1/6	
20		0/6	
40		0/6	

[a]Male Wistar rats were divided into three groups (n=6 per group), injected i.p. with LPS (10, 20, 30 mg/kg b.w.) i.p. Survival was measured over the 7 days. The dose of LPS that was lethal to 50% of the rats (LD_{50}) was 22.15 mg/kg (95% CI 16.5-29.1). Rats were divided into three groups (n=6 per group) and treated orally with simvastatin (5, 10, 20, or 40 mg/kg/day) for 5 days and then with a single i.p dose of LPS (LD_{50}). Survival of animals was measured over 7 days.

Various doses of simvastatin given prior to LPS challenge resulted in dose-dependent increase in survival. Table 1 shows that complete protection was achieved with 20 and

by sinusoidal hyperemia, vasodilatation and prominent perivascular accumulation of PMNCs. Also, it can be seen a few foci of subcapsular hepatocytes necrosis with PMNC

Table 2. Simvastatin improves survival in rats challenged with lethal doses of LPS. The LD_{50} of LPS in simvastatin group and protective index (PI) for oral simvastatin (20 mg/kg) was established by a five-day pretreatment regimen. One set of rats was divided into three groups (n=6 per group); the animals were challenged i.p with a single lethal dose of LPS (2x, 2,5x or 3x LD_{50}).

Simvastatin (mg/kg/day, p.o.)	LPS (mg/kg, i.p.)	No. of rats (dead/total)	LD_{50} of LPS (95% CI) (mg/kg, i.p.)	PI / ED_{50} (95% CI) (mg/kg, p.o.)
20	2 x LD_{50}	2/6	46, 34 [a] (37, 86 - 56, 74)	2.09 [a]
	2,5 x LD_{50}	4/6		
	3 x LD_{50}	6/6		
5	2 x LD_{50}	6/6	-	14.14 (22, 41 - 8,93) [b]
10		6/6		
20		2/6		
40		0/6		

[a] Next, to determine effective dose (ED_{50}) of orally administered simvastatin, another set of animals was divided into four groups (n=6 per group) and simvastatin was given in doses of 5, 10, 20 or 40 mg/kg/day for five days prior to LPS challenge (2x LD_{50}). [b] Survival rate in both sets of animals was assessed over 7 days. The Lichfield & Wilcoxon procedure was used to calculate the LD_{50} of LPS in simvastatin group, PI and ED_{50} of simvastatin.

infiltration. Most of the hepatocytes (> 50% cells) showed pronounced vacoulisation of cytoplasm and nucleoplasm, and pycnotic nuclei. Severity of liver injury induced by LD_{50} of LPS is estimated as TDS of 3.67 (SD = 0.55) (Table 3).

Pretreatment with 20 mg/kg of simvastatin significantly inhibited these pathological changes concomitant with reduction of inflammatory infiltration. (Figure 1C). We noted increased mitotic activity of hepatocytes (mostly with pathological nuclei), vasodilatation and decreased liver damage in sections from animal pretreated with 40 mg/kg of simvastatin. The reduction of inflammatory infiltrate was approximately 50% greater than with 20 mg/kg of simvastatin, suggesting that the protective and anti-inflammatory effects are dose-dependent. Simvastatin (40 mg/kg) significantly decreased TDS compared to that of the untreated group (p< 0.001) (Table 3).

Immunohistochemical detection of cleaved caspase-3. Because hepatocellular apoptosis is a hallmark of endotoxin-induced liver damage, we assessed liver cell apoptosis in stained tissue sections and measured cleaved caspase-3 immunohistochemically. As expected, we found that the calculated LPS LD_{50} increased apoptosis of centrilobular hepatocytes, which can be identified by moderate cytoplasmatic staining (Figure 2A and 2B). Moderate nuclear and/or cytoplasmatic staining of cleaved caspase-3 was also detected in resident liver macrophages located within the sinusoidal spaces (Kupffer cells). Notably, administration of simvastatin decreased endotoxin-induced apoptosis of macrophages as well as hepatocytic cell death by attenuating expression of cleaved caspase-3. (Figure 2C), which is stained immunohistochemically for cleaved caspase-3, shows only weakly stained immune cells and negative or unstained hepatocytes.

Table 3. Effects of simvastatin on the tissue damage score (TDS) in LPS induced liver injury. Effects of oral simvastatin pretreatment (10, 20 and 40 mg/kg) on TDS were evaluated 7 days after a single dose of LPS (LD_{50}) and compared to TDS in group treated with LPS alone or control group. The TDS was determined in six randomly selected visual fields (40x) from tissue sections of each liver. TDS was graded on a scale of 0–5, based on the amount of inflammatory cells, hemorrhages and oedema as well as the number of foci involved.

Drugs	TDS (6 liver samples x 6 sections)					Values are mean (SD)
	0	1	2	3	4	
Control[1]	36	0	0	0	0	0
LD_{50} LPS	0	0	0	13	23	3.67 (0.55)[2]
Simvastatin, 10 mg/kg	0	0	12	24	0	2.67 (0.52)[3]
Simvastatin, 20 mg/kg	0	12	14	10	0	2.00 (0.89)[3,4]
Simvastatin, 40 mg/kg	0	15	21	0	0	1.5 (0.55)[4]

§ [1]Saline (1 mL/kg). The differences in TDS between groups were statistically analyzed using the Kruskal–Wallis rank test and results were expressed in X (SD) [2]$p < 0.001$ versus control, [3]$p < 0.05$ versus control, [4]$p < 0.001$ versus LD_{50} LPS.

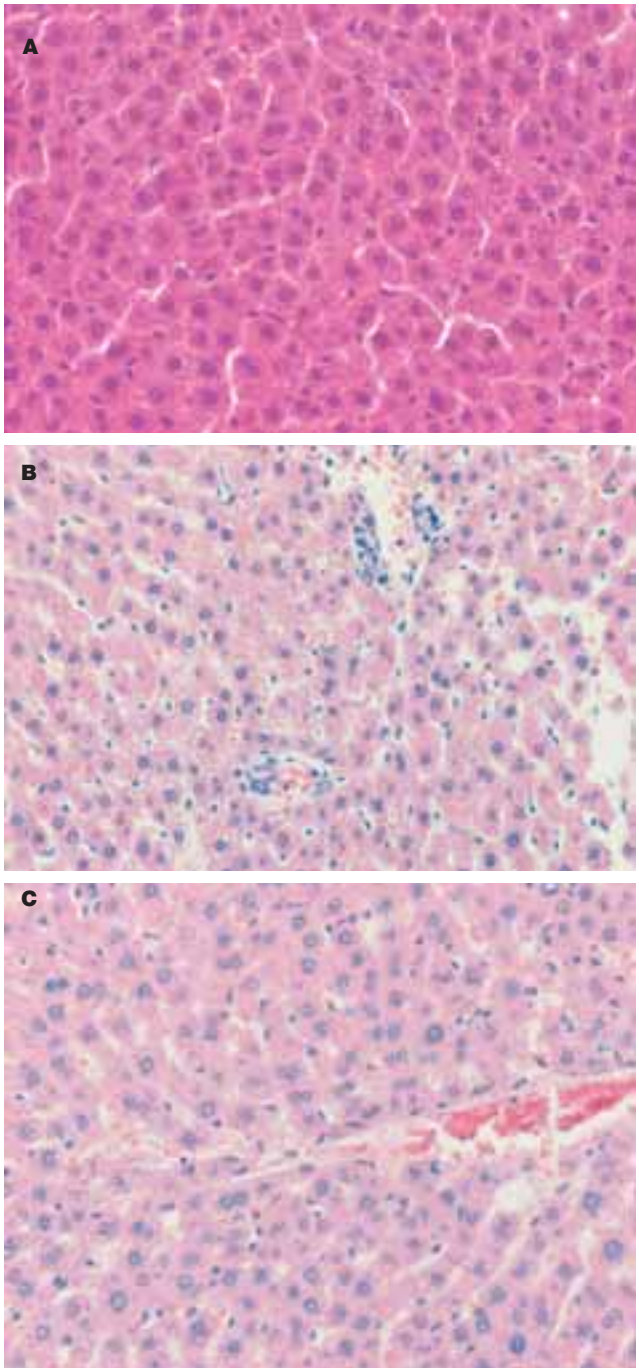


Figure 1. Simvastatin protects against pathological changes in the liver induced by LPS.

Representative section from each group of six rats (haematoxylin and eosin staining, magnification 20x). **A** = Control (untreated) rat. **B** = LPS challenged rat (LD_{50}) showing sinusoidal hyperemia, prominent infiltration of PNMC, local necrotic foci, with moderate disorganization of liver architecture. **C** = Pretreatment with simvastatin (20 mg/kg, orally) before the single LD_{50} of LPS; note the significant reduction in inflammatory infiltrates compared to **B**.

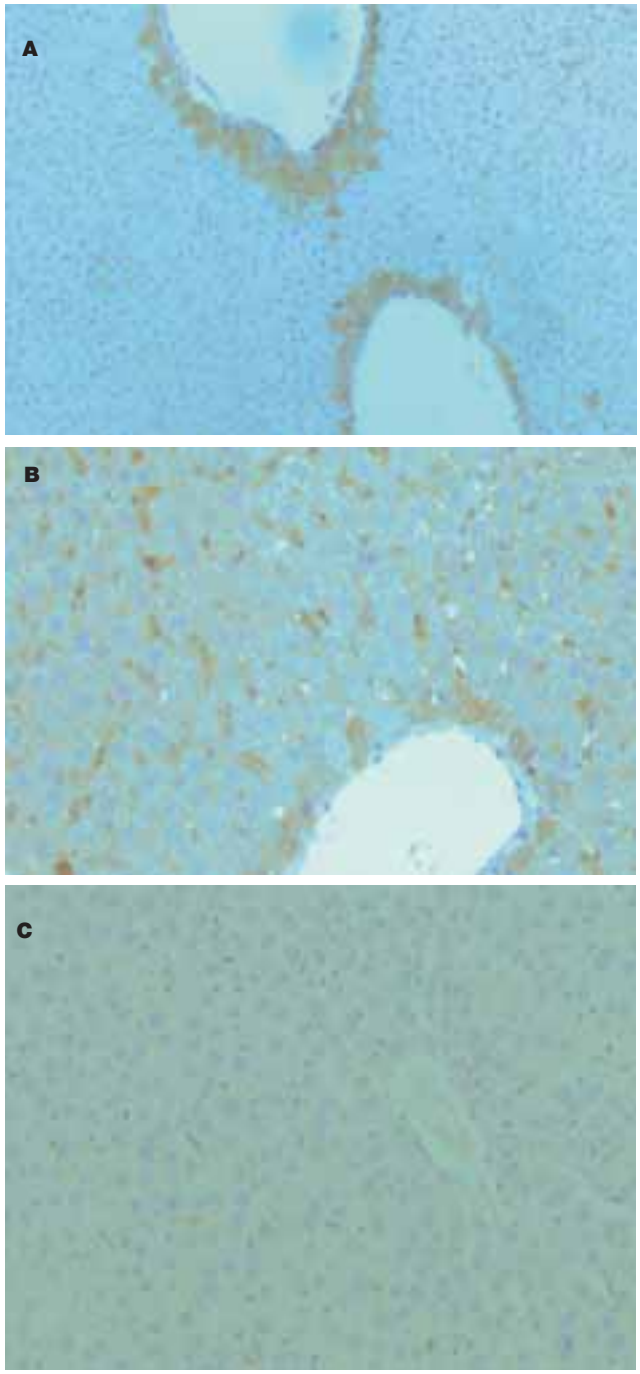


Figure 2. Immunohistochemical detection of liver cell apoptosis in endotoxic shock.

A. Cytoplasmatic staining for cleaved caspase-3 in hepatocytes from rats treated with single LD_{50} of LPS (x10 magnification); B. Nuclear and/or cytoplasmatic staining for cleaved caspase-3 in Kupffer cells from rats treated with single LD_{50} of LPS (x20 magnification). C. Weak staining of Kupffer` cells and unstained hepatocytes from rats pretreated with simvastatin 20 mg/kg before the single LD_{50} of LPS (x20 magnification).

Discussion

We find that orally administered simvastatin, in doses comparable to those used in clinical practice, significantly improves survival in a rat model of endotoxic shock and protects the animals from endotoxin-induced liver injury. Pretreatment with simvastatin markedly reduced intrahepatic infiltration of leukocytes as well as hepatocellular apoptosis in endotoxemic rats.

Statins have potent anti-inflammatory actions that appear to be independent of their effect on cholesterol metabolism.[11,13,15,16] These drugs are reported to decrease sepsis-induced mortality, although the protective mechanisms remain elusive.[20,21] Several studies in a murine model of endotoxic shock suggest that simvastatin improves survival and protects against endotoxin-induced multiple organ injury, including kidney and liver failure.[5,7,22] Various studies confirm that statins suppress release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6),[4,22] stimulate production of anti-inflammatory biomarkers (IL-10, NO) [5,22] and decrease markers of organ injury associated with endotoxic shock.[5,7,22]

Current research indicates that statins may protect against endotoxin-induced hepatotoxicity via a HMG-CoA reductase-dependent mechanism. For example, Slotta et al.[7] found that co-administration of mevalonate with simvastatin almost completely reversed the protective effect of the statin on endotoxin-induced liver injury, suggesting participation of HMG-CoA reductase-dependent pathways. HMG-CoA reductase-independent effects of statins on endotoxemic liver injury remain to be documented.

Leukocyte recruitment and extravascular accumulation are key components in both host-defense reactions and in organ injury. Because leukocyte recruitment is an early and rate-limiting step in endotoxin-induced liver injury,[8,9] we examined the effect of simavastatin on intrahepatic infiltration of leukocytes in animals challenged with sublethal and lethal doses of endotoxin. The results, expressed as TDS, indicate that simvastatin significantly reduced endotoxin-provoked infiltration of leukocytes and deterioration of normal structure in a dose-related manner. This observation extends previous studies that reported attenuation by statins of leukocyte infiltration into the brain,[23] retina,[23] heart[22], and synovium.[24] The data further indicate that leukocyte accumulation in the liver responds to treatment with statins. These drugs inhibit LFA-1, a key adhesion molecule that influences endotoxin-induced leukocyte recruitment and liver damage by binding to a regulatory site on LFA-1.[25] Moreover, statins also inhibit a number of critical points in endotoxin-induced leukocyte recruitment and tissue injury. These include the expression of specific adhesion molecules, such as P-selectin[8] and intercellular adhesion molecule-1,[9]as well as generation of hepatic chemokines.[11]

Hepatocyte apoptosis is a prominent and important feature in endotoxemic liver injury, and over-production of TNF-α appears to trigger the extrinsic pathway of apoptosis.[26] These findings are in accord with our previous study,[4] where we found increased production of TNF-α in endotoxemic rats. Hepatocyte apoptosis may be an end-stage of endotoxin-induced liver injury, but it may also signal early changes in endotoxemic hepatotoxicity. Fouzi and associates[27] found that activation of a membrane receptor Fas (from superfamily of TNF receptors) causes apoptosis and generates chemokines and inflammation in the liver. Furthermore, endotoxin may trigger apoptosis even before the onset of leukocyte recruitment.[28]

In contrast, inhibition of chemokines and specific adhesion molecules expression decreases endotoxin-induced apoptosis via attenuation of PMNC infiltration. Together, these findings indicate that endotoxin-induced liver injury involves a complex interplay between inflammation, necrosis and apoptosis. In this escalating cascade, necrotic and apoptotic cells also enhance recruitment of leukocytes, while, in turn, accumulating inflammatory cells reinforce further hepatocellular apoptosis.[8]

In this study, we noted a significant increase in hepatocytes with characteristic nuclear morphological hallmarks of programmed cell death, such as nuclear pycnosis and karyorrhexis. These findings mirrored the increase in caspase-3 activity in the liver. Simvastatin treatment markedly reduced endotoxin-induced increases in caspase-3 activity and apoptosis of liver hepatocytes and macrophages. Slotta et al.[7] reported that anti-apoptotic activity of simvastatin was reversed by co-injection of mevalonate. Their results suggest that the protective action of the statin depends upon HMG-CoA reductase regulation of programmed cell death in endotoxemic liver injury.

While we used endotoxin (LPS) to initiate acute, severe inflammation and endotoxic or septic shock, our rat model lacks an infection site commonly seen in clinical cases of endotoxic shock; it uses just one of many ways to activate the immune system. Our technique caused an acute, short-lived activation, not the extended inflammatory state where pro-inflammatory cytokines persist in circulation, as occurs with multiple organ injury. The animal species and the endotoxin dose (rodents are resistant to endotoxin and thus require higher doses than humans), as well as the dose and duration of simvastatin treatment, could also affect the results.[29]

Nonetheless, for this particular model, oral simvastatin exhibits protective and anti-inflammatory effects. It inhibits endotoxin-provoked inflammatory infiltration and deterioration of the liver, including apoptosis of hepatocytes and macrophages, suggesting that therapy with simvastatin or other agents that directly target HMG-CoA reductase could protect the liver against inflammation.

No potential conflict of interest relevant to this article was reported.

References

1. Gao F,Linhartova L, Johnston AM, Thickett DR. Statins and sepsis. Br J Anaesth 2008;100:288–98.
2. Ando H, Takamura T, Ota T, Nagai Y, Kobayashi K. Cerivastatin improves survival of mice with lipopolysaccharide induced sepsis. J Pharmacol Exp Ther 2000;294:1043–6.
3. Yasuda H, Yuen PS, Hu X, Zhou H, Star RA. Simvastatin improves sepsis-induced mortality and acute kidney injury *via* renal vascular effects. Kidney Int 2006;69:1535–42.
4. Nežić L, Škrbić R, Dobrić S, Stojiljković MP, Milovanović Z, Jaćević V. et al. Effect of simvastatin on proinflammatory cytokines production in rats during lipopolysaccharide-induced inflammation. Gen Physiol Biophys 2009;Spec No:119-26.
5. Chaudhry MZ, Wang JH, Blankson S, Redmond HP. Statin (cerivastatin) protects mice against sepsis-related death *via* reduced proinflammatory cytokines and enhanced bacterial clearance. Surg Infect (Larchmt) 2008;9:183–94.
6. Holman JM, Saba TM. Hepatocyte injury during post-operative sepsis: activated neutrophils as potential mediators. J Leukoc Biol 1998;43:193-203.
7. Slotta JE, Laschke MW, Wang Y, Schilling MK, Menger MD, Thorlacius H. Inhibition of HMG-CoA reductase reduces leukocyte recruitment and hepatocyte apoptosis in endotoxin-induced liver injury. J Investig Med 2009;5:645-9.
8. Klintman D, Li X, Thorlacius H. Important role of P-selectin for leukocyte recruitment, hepatocellular injury, and apoptosis in endotoxemic mice. Clin Diagn Lab Immunol 2004;11:56-62.
9. Klintman D, Schramm R, Menger MD. Leukocyte recruitment in hepatic injury: selectin-mediated leukocyte rolling is a prerequisite for CD18-dependent firm adhesion. J Hepatol 2002;36:53-9.
10. Wong J, Johnston B, Lee SS, Bullared DC, Smith CV, Beaudet AL. et al. A minimal role for selectins in the recruitment of leukocytes into the inflamed liver microvasculature. J Clin Invest 1997;99:2782-90.
11. Li X, Klintman D, Weitz-Schmidt G, Schramm R, Thoralacius. Lymphocyte function antigen-1 mediates leukocyte adhesion and subsequent liver damage in endotoxemic mice. Br J Pharmacol 2004;141:709-16.
12. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. Arterioscler Thromb Vasc Biol 2001; 21:1712–9.
13. Pierre-Paul D, Gahtan V. Noncholesterol-lowering effects of statins. Vasc Endovasc Surg 2003; 37:301–13.
14. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark lT, Hunninghake DB. et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines, Arterioscler Thromb Vasc Biol 2004;24:149–61.
15. Falagas ME, Makris GC, Matthaiou DK, Rafailidis PI. Statins for infection and sepsis: a systematic review of the clinical evidence, J. Antimicrob.Chemother 2008;61:774–85.
16. Merx MW, Liehn EA, Graf J, van de Sandt A, Schaltenbrand M, Schrader J. et al. Statin treatment after onset of sepsis in a murine model improves survival. Circulation 2005;112:117–24.
17. Litchfield JT, Wilcoxon F. A simplified method of evaluating dose effective experiments. J Pharmacol Exp Ther 1949;96:99–113.
18. Garip S, Severcan F. Determination of simvastatin-induced changes in bone composition and structure by Fourier transform infrared spectroscopy in rat animal model. J Pharma Biomed Analysis 2010;52:580–8.
19. The Human Protein Atlas. [home page on the Internet]: Knut & Alice Wallenberg foundation. Available from http://www.proteinatlas.org/ ENSG00000164305/normal
20. Dobesh PP, Klepser DG, McGuire TR, Morgan CW, Olsen KM. Reduction in mortality associated with statin therapy in patients with severe sepsis. Pharmacotherapy 2009;29:621-30.
21. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. Respir Res 2005;6:82-9.
22. Chung HC, Lee RP, Wu WT, Liao KW, Hsu N, Hsu BG. Fluvastatin ameliorates endotoxin induced multiple organ failure in conscious rats. Resuscitation 2007; 74:166-74.
23. Weitz-Schmidt G. Statins as anti-inflammatory agents. Trends Pharmacol Sci 2002;23:482-6.
24. Naidu BV, Woolley SM, Farivar AS, Thomas R, Fraga C, Mulligan MS. Simvastatin ameliorates injury in an experimental model of lung ischemia-reperfusion. J Thorac Cardiovasc Surg 2003;126:482-9.
25. Weitz-Schmidt G, Welzenbach K, Dawson J, Kallen J. Improved lymphocyte function-associated antigen-1 (LFA-1) inhibition by statin derivatives: molecular basis determined by x-ray analysis and monitoring of LFA-1 conformational changes in vitro and ex vivo. J Biol Chem 2004;*279(45):46764-71.*
26. Mahidhara R, Billiar TR. Apoptosis in sepsis. Crit Care Med 2000;28:N105-13.
27. Faouzi S, Burckhardt BE, Hanson JC, Campe CB, Schrum LW, Rippe RA. et al. Anti-Fas induces hepatic chemokines and promotes inflammation by an NF-κB-independent, caspase-3-dependent pathway. J Biol Chem 2001;276,49077-82.
28. Lawson JA, Fisher MA, Simmons CA, Farhood A, Jaeschke H. Parenchymal cell apoptosis as a signal for sinusoidal sequestration and transendothelial migration of neutrophils in murine models of endotoxin and Fas-antibody-induced liver injury. Hepatology 1998;28:761-7.
29. Poli de Figueiredo LF, Garrido AG Nakagawa N, Sannomiya P. Experimental models of sepsis and their clinical relevance. Shock 2008; 30, Suppl 1:53-9.

ORIGINALNI ČLANAK

Sindrom sagorijevanja na poslu specijalizanata porodične medicine

Kosana Stanetić [1], Gordana Tešanović [1], Marija Burgić-Radmanović[2]

[1] Dom zdravlja Banja Luka, Katedra porodične medicine, Medicinski fakultet, 78000 Banja Luka

[2] Klinika za psihijatriju, Klinički centar Banja Luka, 78000 Banja Luka

Kontakt osoba:
Dr Kosana Stanetić
Tel: 051 211 177
Mob. Tel: 065 535 790
Email: mirkos@inecco.net

APSTRAKT

Cilj istraživanja je bio da se ispita prevalenca sindroma sagorijevanja na poslu kod ljekara na specijalizaciji iz porodične medicine u Republici Srpskoj u odnosu na pol, bračni status i broj djece. Istraživanje je provedeno anketiranjem ljekara na specijalizaciji iz porodične medicine u edukativnim centrima porodične medicine Banja Luka i Doboj u periodu od 1. februara do 30. aprila 2010. godine. Ispitanici su popunjavali anketni upitnik za samoprocjenu nivoa stresa i 'Maslach Burnout Inventory' koji su bili dopunjeni podacima o dobi, polu, bračnom stanju i broju djece sa kojima žive. Istraživanjem je obuhvaćeno 57 ljekara, od kojih je bilo 20 muškaraca. Visok nivo stresa imalo je 77.2% ljekara. Ispitanici su imali umjeren nivo emocionalne iscrpljenosti i depersonalizacije. Kod ljekara-žena, izražen je umjeren, a kod ljekara-muškaraca niži nivo ličnog zadovoljstva; ali među ovim grupama ispitanika nije nađena statistički značajna razlika. Rezultati istraživanja nisu pokazali da postoji povezanost između pola, bračnog stanja, uključujući i broj djece u porodici, na pojavu sindroma sagorijevanja na poslu.

KLJUČNE RIJEČI

sindrom sagorijevanja na poslu, specijalizanti, bračno stanje, djeca u porodici

(Scr Med 2011;42:14-7)

Submitted: February 10, 2011
Accepted: April 22, 2011

Sindrom sagorijevanja na poslu (eng. "burnout syndrome") je odgovor na dugotrajne hronične emocionalne i međuljudske stresore koji su povezani sa radnim mjestom. Prema definiciji koju su 1996. godine postavili Girdiano, Everly i Dusek[1] , sindrom sagorijevanja na poslu je stanje dugotrajne psihičke, fizičke i emocionalne iscrpljenosti uzrokovane pretjeranim i prolongiranim stresom. Neusaglašenost odnosa zaposlenih ljudi sa jedne i radne sredine sa druge strane mogu dovesti do ovog poremećaja koji se definiše kao hronični radni stres u koji su uključeni: osjećaj emocionalne iscrpljenosti, depersonalizacija i osjećaj smanjenog ličnog zadovoljstva. Sindrom se najčešće javlja kod osoba koje rade u direktnom kontaktu sa drugim ljudima,[2-4] a ljekari su jedna od profesija s najvećim rizikom.[5,6]

Brojna su istraživanja o zastupljenosti sindroma sagorijevanja na poslu kod ljekara na specijalizaciji. Tako je pokazano[7] da je sindrom prisutan kod oko 50% ljekara na specijalizaciji u SAD; najviše je bio zastupljen kod ljekara na specijalizaciji iz ginekologije i akušerstva (75%), a najmanje kod ljekara na specijalizaciji iz porodične medicine (27%). Studija provedena u Grčkoj na 311 specijalizanata pokazala je da umjerene i teške simptome sindroma sagorijevanja na poslu ima 154 (49.5%) ispitanika.[8] Nezadovoljsvo sistemom specijalizacije glavni je uzrok visoke prevalence ovog sindroma u pomenutom istraživanju. Brojna istraživanja o prisustvu i uzrocima sindroma sagorijevanja na poslu kod ljekara na specijalizaciji koja su provedena od 1983. do 2004. godine pokazuju da intenzivan rad, nedostatak vremena za odmor i socijalne kontakte van posla predstavljaju najvažnije predisponirajuće faktore za razvoj ovog sindroma kod ljekara na specijalizaciji.[9]

Cilj ovog istraživanja je bio da se ispita prevalenca sindroma sagorijevanja na poslu kod ljekara na specijalizaciji iz porodične medicine u Republici Srpskoj u odnosu na pol, bračni status i broj djece sa kojima ispitanici žive.

Metode

Istraživanje je provedeno anketiranjem ljekara na specijalizaciji iz porodične medicine u edukativnim centrima porodične medicine Banja Luka i Doboj u periodu od 1. februara do 30. aprila 2010. godine. Ljekarima koji su u to vrijeme bili na specijalizaciji iz porodične medicine ponuđen je anketni upitnik koji je sadržavao pitanja koja su formulisana prema poznatim upitnicima za samoprocjenu

nivoa stresa[1] i *Maslach Burnout Inventory*.[6] Naš upitnik je dopunjen podacima o dobi, polu, bračnom statusu i broju djece sa kojima ispitanici žive. Anketa je bila anonimna, a ispitanici su samostalno popunjavali anketni upitnik.

Za statističku analizu korišteni su *t*-test ili χ^2 test, a nivo značajnosti je bio $p<0.05$.

Mjerenja. Upitnik za samoprocjenu nivoa stresa sadrži deset pitanja. Maksimalan broj bodova je 40, a ispitanici koji imaju između 25 i 40 bodova su stanju visokog nivoa stresa. Anketni upitnik *Maslach Burnout Inventory* sadrži 22 pitanja na koja su odgovori bodovani Likertovom skalom od 0 do 6 da se odrede ove psihičke dimenzije: emocionalna iscrpljenost (EI), depersonalizacija (DP) i lično zadovoljstvo (LZ). EI se procjenjuje odgovorima na 9 pitanja, a maksimalan broj bodova je 54 (zbir bodova < 17 pokazuje nizak, 18-29 umjeren, >30 visok nivo emocionalne iscrpljenosti). DP se testira pomoću 5 pitanja, a maksimalan broj bodova je 30 (zbir bodova <5 pokazuje nizak, 6-11 umjeren, >12 visok nivo depersonalizacije), a LZ se procjenjuje na osnovu odgovora na 8 pitanja; maksimalan broj bodova je 48 (zbir bodova <33 pokazuje visok, 34-39 umjeren, >40 nizak nivo ličnog zadovoljstva).

Rezultati

Od 69 distribuiranih anketnih upitnika popunjeno je i analizirano 57; 20 (35.1%) muškog i 37 (64.9 %) ženskog pola. Prosječna starost anketiranih ljekara bila je 37.3 (SD=6.94). Najmlađi ispitanik imao je 27, a najstariji 55 godina. U grupi anketiranih ljekara bilo je 34 oženjenih/udatih. Bez djece je bilo 24, a jedno ili više djece imalo je 33 anketirana ljekara.

Visok nivo stresa je ustanovljen kod 44 (77.2%) ispitanika (Tab. 1). Ljekari ženskog pola imali su viši nivo stresa od muških ispitanika (62.2%, odnosno 55.0%), ali ta razlika nije statistički signifikantna. Srednje vrijednosti emocionalne iscrpljenosti kod ljekara ženskog pola su bile 22.46 (SD=2.2), a kod ispitanika muškog pola 21.3 (SD=2.9). Ta razlika nije statistički signifikantana (p=0.702).

Nivo emocionalne iscrpljenosti, depersonalizacije i ličnog zadovoljstva kod ženskih i muških ispitanika je prikazan na Tabeli 1. Razlike među polovima nisu ni statistički ni klinički značajne.

Kod ljekara koji žive u braku, srednja vrijednost za emocionalnu iscrpljenost iznosila je 23.8 (SD=2.4), depersonalizaciju 7.8 (SD=1.1) i lično zadovoljstvo 39.6 (SD=1.1) bodova. Kod neoženjenih/neudatih srednja vrijednost emocionalne iscrpljenosti iznosila je 19.4 (SD=2.2) boda, a kod depersonalizacije 6.8 (SD=1.0) i ličnog zadovoljstva 38.9 (SD=1.4) bodova. Ove razlike među ispitanicima koje se odnose na bračni status nisu statistički značajne.

Kod ispitanika koji nisu imali djecu nađene su srednje vrijednosti emocionalne iscrpljenosti 19.4 (SD=2.1), depersonalizacije 6.6 (SD=1.0) i ličnog zadovoljstva 39.1 (SD=1.4) bodova. Kod anketiranih ljekara koji su imali jedno dijete ili više djece te vrijednosti su iznosile za emocionalnu iscrpljenost 24.0 (SD=2.5), depersonalizaciju 8.1 (SD=1.1) i lično zadovoljstvo 39.5 (SD=1.1). Ni jedna razlika tri psihičke dimenzije između ispitanika koji su imali djecu i onih bez djece nije bila statistički signifikantna.

Diskusija

Rezultati ovog istraživanja pokazuju da visok procenat (77.2%) anketiranih ljekara na specijalizaciji ima visok nivo stresa. Anketirani ljekari oba pola imaju umjeren stepen emocionalne iscrpljenosti i depersonalizacije, dok ljekari ženskog pola imaju umjeren stepen, a ljekari muškog pola nesto niži stepen ličnog zadovoljstva.

U preglednom članku koji obuhvata više istraživanja o sindromu sagorijevanja na poslu kod ljekara na specijalizaciji[9] nije ustanovljeno da postoji značajna razlika između ispitanika muškog i ženskog pola. Međutim, Geurtis i sar.[10] su ustanovili da ljekari ženskog pola imaju veći stepen emocionalne iscrpljenosti, dok u nivoima depersonalizacije među polovima nije bilo razlike.

Rezultati ostalih istraživanja pokazaju da su sociodemografska obilježja (pol, bračni status ili broj djece) povezani

Tabela 1. Nivo stresa, emocionalne iscrpljenosti, depersonalizacije i ličnog zadovoljstva kod ispitanika

	Muškarci	Žene
Visok nivo stresa	55.0%	62.2%
Emocionalna iscrpljenost	21.3 (SD=2.89)*	22.5 (SD=2.17)
Depersonalizacija	7.5 (SD=1.35)	7.4 (SD=1.18)
Lično zadovoljstvo	40.7 (SD=1.12)	38.6 (SD=1.18)

***Srednja vrednost; SD-standardna devijacija. Među polovima nije nađena signifikantna razlika.**

sa pojavom sindroma sagorijevanja na poslu, a roditeljstvo se smatra kao protektivni faktor.[11] Woodside i sar.[12] su ustanovili da specijalizanti ženskog pola imaju manje izražene simptome depersonalizacije u odnosu na specijalizante muškog pola, a da specijalizanti u čijim je porodicama bilo djece imaju niži stepen depersonalizacije i emocionalne iscrpljenosti. Međutim, kod specijalizanata porodične medicine u Zagrebu nije nađena značajna razlika između anketiranih u nekoj od subskala ovog sindroma u odnosu na njihova sociodemografska obilježja.[13] Ni istraživanje Martinija i saradnika[14] nije pokazalo da roditeljstvo utiče na pojavu sindroma sagorijevanja na poslu kod ljekara na specijalizaciji iz porodične medicine, ali je Lemkau[15] ustanovio da roditeljstvo dovodi do nižeg stepena depersonalizacije. U našem istraživanju nije nađena povezanost između stepena sindroma sagorijevanja na poslu u odnosu na pol, bračni status i roditeljstvo u bilo kojoj podskali sindroma.

Naporan program specijalizacije, pripreme za specijalistički ispit, odvajanje od porodice, promjena životne i radne sredine za vrijeme specijalizacije i lična finansijska situacija vjerovatno su uzrok visokog nivoa stresa i simptoma sindroma sagorijevanja na poslu kod ljekara specijalizanata porodicne medicine. Prosječna starost specijalizanata u našem istraživanju je preko 37 godina, što ukazuje da bi i godine mogle biti uzrok težem podnošenju obaveza specijalizacije. Zato bi vrijedilo detaljnije istražiti uticaj svih pomenutih faktora na sagorijevanje na poslu, a možda i one faktore koji se odnose na specificne društveno-ekonomske prilike u regionu koje su nastale u vrijeme nedavnog rata i tokom poslijeratnog perioda.

Samopomoć i briga o sebi nije dio profesionalne edukacije ljekara i uglavnom zauzima veoma nisko mjesto na listi prioriteta ljekara-specijalizanata. U Švajcarskoj 21% ljekara u primarnoj zdravstvenoj zaštiti nema svog porodičnog ljekara, a 90% vrši samoliječenje.[16] U istraživanju Kumbrije i saradnika čak 62.9% ljekara porodične medicine u Hrvatskoj nije imalo svog izabranog ljekara već se liječilo samostalno.[17] U svom poslu ljekari se bave problemima drugih ljudi po cijeli dan, tako da imaju malo vremena za rješavanje svojih vlastitih problema.[5] Rezultati našeg, ali i drugih istraživanja ukazuju na potrebu edukacije ljekara na specijalizaciji o prevenciji i metodama za prevazilaženje stresa i sindroma sagorijevanja na poslu.

Autori ovog članka nisu deklarisali konflikt interesa u vezi s ovim istraživanjem.

Reference

1. Girdin DA, Everly GS, Dusek DE. Controlling stress and tension. Needham Heights, Allyn and Bacon,1996.
2. Michaels RM. Physician burnout. Pennsyl Med 1996; 99:18-21.
3. Maslach C, Schaufeli W, Leiter MP. Job burnout. Ann Rev Psychol 2001; 52: 397-422.
4. Peterson U. Stress and burnout in healthcare workers. Stockholm, Karolinska Institutet, 2008.
5. Guderson L. Physician burnout. Anal Int Med 2001; 135:145-8.
6. Maslach C, Jackson SE, Leiter MP. MBI: The Maslach burnout inventory: Manual. Palo Alto, Consulting Psychologists Press, 1996.
7. Martini S, Arfken CI, Churchill A, Balon R. Burnout comparison among residents in different medical specialties. Acad Psychiatry 2004; 28:240-2.
8. Msaouel P, Keramaris NC, Tasoulis A, Kolokythas D, Syrmos N, Pararas E, Thireos E, Lionis C. Burnout and training satisfaction of medical residents in Greece: will the European work time directive make a difference? Hum Resour Health 2010. Published online doi:10.1186/1478-4491-8-16.
9. Thomas NK. Resident burnout. JAMA 2004;292:2880–9.
10. Geurts S, Rutte C, Peeters M. Antecedents and consequences of work-home interference among medical residents. Soc Sci Med 1999;48:1135-48.
11. European General Practice Research Network Burnout Study Group. Burnout in European family doctors: the EPGRN study. Fam Pract 2008;25:245-65.
12. Woodside JR, Miller MN, Floyd MR, McGowen KR, Pfortmiller DT. Observation on burnout in family medicine and psychiatry residents. Acad Psychiatry 2008;32:13-9.
13. Tušek S, Ožvačić Z, Polašek O, Katić M. Izloženost specijalizanata obiteljske medicine sindromu izgaranja na poslu. Med Fam Croat 2010;2:8-17.
14. Martini S, Arfken CL, Churchill A, et al. Burnout comparison among residents in different medical specialities. Acad Psychiatry 2004; 28:240-2.
15. Lemkau J, Rafferty J, Gordon RJ. Burnout and career-choice regent among family practice physicians in early practice. Fam Pract Res J 1994; 14:213-22.
16. Schneider M, Bouvier Gallacchi M, Goehring C, et al. Personal use of medical care and drugs among Swiss primary care physicians. Swiss Med Wkly 2007;137:121-6.
17. Kumbrija S, Blažeković-Milaković S, Doko-Jelinić J, et al. Zdravstveni radnici-odnos prema vlastitom zdravlju. Acta Med Croatica 2007;61:105-10.

Prevalence of Burnout Syndrome Among Family Medicine Residents

Kosana Stanetić, Gordana Tešanović, Marija Burgić-Radmanović

ABSTRACT

A survey in the form of a questionnaire assessed the prevalence of the burnout syndrome among family medicine residents in the Republic of Srpska. The survey considered gender, marital status, and number of children in the family of participants. This study was based upon results of a survey questionnaire that was distributed to family medicine residents in the Educational Centers of Family Medicine, Banja Luka and Doboj, during the period from February 1 to April 30, 2010. Participants answered the self-assessment questionnaire regarding stress level and also the Maslach Burnout Inventory questionnaire that provided data regarding age, sex, marital status and the number of children in family. The respondents included 57 physicians, 20 male and 37 female, all of whom were residents in family practice. More than three fourths (77.2 %) of the respondents had a high level of stress. Furthermore, the residents had moderate levels of emotional exhaustion and depersonalization. Female residents reported only moderate levels of personal accomplishment, while male physicians had lower levels. There was no statistically significant difference between data from the male and female groups. The results of the survey failed to establish any correlation between gender, marital status, including the number of children per family, and the prevalence of the burnout syndrome.

KEY WORDS

burnout syndrome, residents, marital status, number of children per family.

ORIGINALNI ČLANAK

Uticaj edukacije za timove porodične medicine na zadovoljstvo pacijenata

Nataša Pilipović-Broćeta[1,2], Gordana Tešanović[1,2], Amela Lolić[3], Jasminka Vučković[3], Nevena Todorović[1,2], Ljubiša Preradović[4]

[1]Javno zdravstvena ustanova Dom zdravlja Banja Luka
[2]Katedra porodične medicine, Medicinski fakultet Univerziteta u Banjoj Luci
[3]Ministarstvo zdravlja i socijalne zaštite Republike Srpske, Banja Luka
[4]Arhitektonsko-građevinski fakultet Univerziteta u Banjoj Luci

Kontakt osoba:
Dr Nataša Pilipović-Broćeta
JZU Dom zdravlja Banja Luka
Sime Matavulja bb
78000 Banja Luka
Bosnia and Herzegovina
Email: npilipovicbroceta@yahoo.com

APSTRAKT

Uvod. Praćenje zadovoljstva pacijenata zdravstvenom zaštitom vrši se u cilju ocjenjivanja kvaliteta i poboljšanja zdravstvene zaštite. Do sada nije objavljeno istraživanje zadovoljstva pacijenata primarnom zdravstvenom zaštitom (PZZ) u Republici Srpskoj. Cilj istraživanja je da se procijene stavovi pacijenata i zadovoljstvo radom na nivou PZZ u Republici Srpskoj. Pored toga, željeli smo uporediti stavove pacijenata koji se liječe kod timova porodične medicine (TPM) i onih koji nisu edukovani u oblasti porodične medicine.

Metode. Anketirali smo 2146 pacijenata u 21 mjestu Republike Srpske, primjenom EuroPep upitnika. Ukupan broj distribuiranih upitnika je bio 2200, a nepopunjenih upitnika je bilo 54.

Rezultati. Rezultati pokazuju da su pacijenti dodijelili više dobrih ocjena edukovanim doktorima, nego onima koji nisu obavili proces edukacije iz porodične medicine. Bolje ocjene su date TPM na pitanja koja se odnose na oporavak od bolesti, povratak na posao, emocionalne probleme i kontakt pacijent-doktor.

Zaključak. Organizacija službe na nivou PZZ u Republici Srpskoj je pozitivno ocijenjena od strane anketiranih. Pacijenti su zadovoljniji radom TPM, gdje su i doktori i sestre obavili edukativni proces. Anketiranima naročito pogoduje sistem naručivanja posjeta, telefonska komunikacija sa porodičnim doktorom, kao i pružanje dodatnih informacija. Ovo istraživanje pokazuje da je edukacija u oblasti porodične medicine korisna.

KLJUČNE RIJEČI

tim porodične medicine, edukacija, EuroPep upitnik, zadovoljstvo pacijenata

(Scr Med 2011;42:18-21)

Submitted: February 10, 2011
Accepted: April 22, 2011

Praćenje zadovoljstva pacijenata zdravstvenom zaštitom vrši se u cilju ocjenjivanja kvaliteta i poboljšanja zdravstvene zaštite. Na zadovoljstvo pacijenata zdravstvenom zaštitom utiču: usluge timova porodične medicine, dostupnost konsultativno-specijalističkih službi, kao i organizacija zdravstvenog sistema u cjelini. Nivo ličnog i kolektivnog zadovoljstva određuju opšte karakteristike pacijenta kao što su: obrazovanje, intelektualne sposobnosti, materijalni i psihofizički status, kao i odnosi u zajednici. Stoga, mišljenje predstavlja promjenljivu vrijednost, pa kao podatak može poslužiti samo u toku kraćeg vremenskog razdoblja.[1] Grol sa saradnicima je vršio istraživanje u 16 evropskih država na uzorku od približno 24 000 pacijenata. Rezultati tog istraživanja su pokazali da je 80% pacijenata dalo najbolje ocjene na pitanja u vezi povjerljivosti medicinske dokumentacije, trajanja pregleda, pažnji usmjerenoj ka pacijentu i rješavanju urgentnih stanja.[2] Iako su rađena neka ispitivanja u organizaciji Fonda zdravstvenog osiguranja, do sada nije objavljeno istraživanje o zadovoljstvu pacijenata uslugama primarne zdravstvene zaštite (PZZ) u Republici Srpskoj.

Cilj istraživanja je da se procijeni zadovoljstvo pacijenata uslugama primarne zdravstvene zaštite u Republici Srpskoj. Pored toga, željeli smo uporediti ocjene pacijenata koji se liječe kod timova porodične medicine (TPM) i onih koji nisu edukovani u oblasti porodične medicine.

Materijal i metode

Tokom perioda od 1.7.2010. do 31.8.2010. godine anketirali smo 2146 pacijenta koji su liječeni na primarnom nivou zdravstvene zaštite u 21 mjestu (Banja Luka, Doboj, Bijeljina, Gradiška, Zvornik, Kozarska Dubica, Trebinje, Derventa, Modriča, Mrkonjić Grad, Pale, Srbac, Ugljevik, Čelinac,

Istočno Sarajevo, Višegrad, Bileća, Gacko, Kneževo, Nevesinje i Srebrenica). Približno polovina od ukupnog broja anketiranih liječena je kod TPM, a drugi dio kod doktora i sestara koji nisu obavili edukaciju u oblasti porodične medicine. Ukupan broj distribuiranih upitnika je bio 2200.

U ovom istraživanju je korišten upitnik koji je izradila Evropska asocijacija za kvalitet u opštoj/porodičnoj medicini (EuroPep upitnik).[2] Njegovom primjenom procjenjuje se rad tima porodične medicine u odnosu na kliničku praksu i organizaciju zdravstvenih usluga. Uvodni dio upitnika odnosi se na pol, dob, broj posjeta doktoru, obrazovni status i subjektivno mišljenje o zdravstvenom stanju. Zatim slijede 23 pitanja vezana za četiri oblasti (O) kvaliteta rada. Prvih šest pitanja obuhvataju odnos sa bolesnikom (O1), sljedećih pet pitanja se odnose na medicinsku brigu (O2), naredna četiri pitanja uključuju oblast informacije i podrške (O3) i posljednjih osam pitanja se odnose na organizaciju rada (O4). Anketirani su davali ocjene od 1 do 5 ili „nije primjenljivo“, u slučaju da se neko od pitanja odnosi na aktivnosti koje se ne obavljaju u okviru njihove odgovarajuće zdravstvene ustanove.

Upitnici su dijeljeni u zdravstvenim ustanovama nakon ljekarskog pregleda/konsultacije ili za sestrinskim pultom, popunjeni i odmah vraćeni. Od ukupnog broja anketiranih, 54 pacijenta ili nisu htjeli da učestvuju u anketi ili nisu propisno popunili upitnike. U uzorak su bili uključeni korisnici zdravstvenih usluga za koje se procijenilo da će biti sposobni da pročitaju, razumiju i popune upitnik. Iz istraživanja bile su isključene osobe mlađe od 18 godina i mentalno oboljele osobe. Osigurana je potpuna anonimnost, sa čime su svi ispitanici prethodno upoznati i objašnjena im je svrha i način popunjavanja upitnika. Nakon prikupljanja svih rezultata urađena je statistička obrada primjenom χ^2 testa, a rezultati su prikazani tabelarno i grafički.

Rezultati

Od ukupnog broja anketiranih (*n*=2146), 52,4% je bilo žena. Kod TPM liječeno je 55,2% pacijenata, a 44,5% kod

Tabela 1. **Prikaz prosječnih ocjena po pitanjima EuroPep testa za TPM i zdravstvene radnike koji nisu završili edukaciju u oblasti porodične medicine**

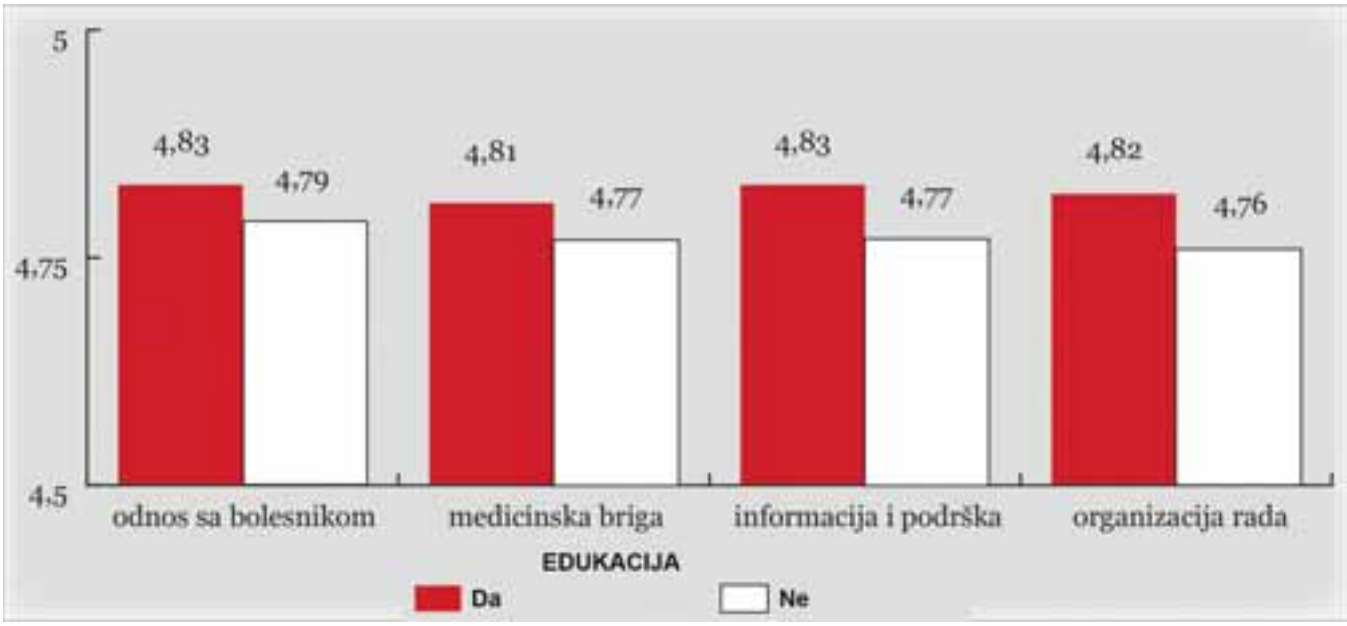
		PITANJE	Edukacija iz porodične medicine	
			Da	Ne
O1	P1.	Smatrate li da Vam Vaš ljekar posvećuje dovoljno vremena tokom pregleda?	4,86	4,83
	P2.	Da li ljekar pokazuje interes za Vaš problem?	4,87	4,83
	P3.	Da li Vam je lakše kada ljekaru kažete svoj problem?	4,81	4,77
	P4.	Da li Vas ljekar uključuje u donošenje odluke o Vašem zdravlju?	4,79	4,74
	P5.	Da li Vas ljekar pažljivo sasluša kada iznosite Vaše probleme?	4,85	4,80
	P6.	Da li Vam daje sve podatke o Vašoj bolesti?	4,82	4,78
O2	P7.	Da li se trudi da Vam što prije olakša Vaše tegobe?	4,84	4,80
	P8.	Da li Vam pomaže da se osjećate bolje i da se što prije vratite svakodnevnom poslu?	4,81	4,76
	P9.	Da li Vaš ljekar pregleda (srce, pluća, uši)?	4,79	4,75
	P10.	Da li je Vaš ljekar temeljit kod pregleda?	4,85	4,79
	P11.	Da li je Vaš ljekar radi na sprječavanju raznih bolesti (prevencija, vakcinacija)?	4,79	4,75
O3	P12.	Da li Vam objašnjava zašto treba da uradite dodatne testove i analize?	4,84	4,79
	P13.	Da li Vam daje objašnjenja o Vašim tegobama i Vašoj bolesti?	4,86	4,80
	P14.	Da li pomaže Vašim emocionalnim problemima vezanim za Vaše zdravlje?	4,78	4,71
	P15.	Da li Vam objašnjava zašto je važno da slijedite njegove/njene uputstva?	4,84	4,80
O4	P16.	Da li se sjeća onoga što je uradio/la ili rekao/la?	4,81	4,77
	P17.	Da li Vam objašnjava šta Vas očekuje prilikom pregleda kod specijaliste?	4,81	4,73
	P18.	Da li Vam pomažu drugi zdravstveni radnici (sestra u ambulanti)?	4,83	4,81
	P19.	Da li možete zakazati pregled kod Vašeg ljekara?	4,86	4,80
	P20.	Da li je lako ostvariti telefonsku vezu sa ljekarom?	4,79	4,71
	P21.	Da li možete tražiti savjete telefonom od ljekara?	4,77	4,71
	P22.	Da li dugo čekate u čekaonici?	4,82	4,71
	P23.	Da li ljekar reaguje brzo u slučaju hitnih stanja?	4,89	4,86

medicinskog osoblja koje nije obavilo edukaciju iz porodične medicine. Od ukupnog broja, 9,7% pacijenata je prvi put došlo na pregled kod TPM, 80,8% je navelo da je u pitanju ponovna posjeta, a 9,4% se nije izjasnilo. Više od polovine anketiranih pacijenata (57,6%) se izjasnilo da im je zdravstveno stanje bilo dobro, 23,5% se izjasnilo da je odlično, 16,3% je bilo lošeg zdravstvenog stanja, a 2,6% se nije izjasnilo.

Prosječna ocjena anketiranih, koji se liječe na primarnom nivou zdravstvene zaštite, odnosi se na srednju vrijednost najboljih ocjena koje su dobili TPM, kao i oni koji nisu završili edukaciju, a rade u domovima zdravlja (Tabela 1).

Rezultati pokazuju da su pacijenti dodijelili bolje ocjene TPM, nego onima koji nisu obavili takav edukativni proces. Posebno je analiza ocjenjivanja četiri oblasti rada pokazala da su pacijenti bolje ocjene dali TPM u navedenim oblastima (Slika 1).

Slika 1. Prikaz srednje vrijednosti ocjene ispitanika po oblastima kvaliteta rada



Analiza odgovora pacijenata prema oblastima kvalitete rada pokazuje veće zadovoljstvo pacijenata sa radom TPM u odnosu na rad onih koji nisu obavili edukaciju.

Najveća razlika u ocjenjivanju dvije navedene grupe zdravstvenih radnika odnosi se na pitanja P8 (p=0,027), P14 (p=0,036), P17 (p=0,002), P21 (p=0,017) i P22 (p=0,011), na koja su bolje ocjene dali pacijenti anketirani kod timova porodične medicine.

Diskusija

Dobijeni rezultati pokazuju da je ocjena zadovoljstva pacijenata uslugama na nivou PZZ dobra, s tim što su anketirani zadovoljniji uslugama pruženim od strane TPM. Sistem porodične medicine je uključio novi način organizacije rada na PZZ, primjenjuje se naručivanje pacijenata na pregled, što se u našem istraživanju pokazalo korisnim i sa čime su pacijenti veoma zadovoljni. Trajanje pregleda je predviđeno na 15 minuta, sa mogućom modifikacijom u zavisnosti od trenutne potrebe pacijenta što je uticalo na povećano zadovoljstvo anketiranih. Na taj način smanjeno je i čekanje na pregled kod TPM, dok kod drugih zdravstvenih radnika pacijenti duže vremena borave u čekaonici.

Pored toga, pacijenti su više zadovoljni sa porodičnim doktorima, jer pokazuju veći interes za probleme pacijenata, naročito emocionalne, vezane za zdravlje pacijenata. Slična istraživanja vršena u Švedskoj pokazala su da je navedeni indikator takođe povećao zadovoljstvo pacijenata.[2,3] Naše istraživanje je pokazalo da tim porodične medicine više pomaže pacijentima da se osjećaju bolje i samim tim da se vrate svakodnevnom poslu.

Zadovoljstvo pacijenata se takođe povećalo zbog pružanja informacija u vezi pregleda kod konsultanata na sekundarnom nivou. Slični nalazi su dobijeni u istraživanju provedenom u Turskoj u 6 gradova na uzorku od 1160 pacijenata, koji se liječe kod 33 tima porodične medicine.[4] Istraživanje u Sloveniji je pokazalo da su pacijenti najviše bili zadovoljni sa porodičnim doktorom, jer je pažljivo saslušao pacijenta, dao sve podatke o bolesti, a takođe je omogućio i naknadnu telefonsku komunikaciju, što je u skladu sa našim nalazima.[5]

Organizacija službe na nivou PZZ u Republici Srpskoj je pozitivno ocijenjena od strane anketiranih. Pacijenti su zadovoljniji radom TPM gdje su i doktori i sestre obavili edukativni proces. Anketiranima naročito pogoduje sistem

naručivanja, telefonska komunikacija sa porodičnim doktorom, kao i pružanje dodatnih informacija. Ovo istraživanje pokazuje da je korisna edukacija u oblasti porodične medicine korisna.

Autori ovog članka nisu deklarisali konflikt interesa u vezi s ovim istraživanjem.

Reference

1. Carr-Hill R. The measurement of patient satisfaction. J Public Health Med 1992;14:236-49.
2. Grol R, Wensing M. Patients in Europe evaluate general practice: an international comparison. Br J Gen Pract 2000;50:882-7.
3. Szecsenyi J, Goetz Katja, Campbell S, Broge B, Reuschenbach B, Wensing M. Is the job satisfaction of primary care team members associated with patient satisfaction? BMJ Qual Saf 2011;20:508-14.
4. Dagdeviren N, Akturk Z. An evaluation of patient satisfaction in Turkey with the EUROPEP instrument. Yonsei Med J. 2004;45:23-8.
5. Kersnik J. Patients' recommendation of doctor as an indicator of patient satisfaction. Hong Kong Med J 2003;9:247-50.

Influence of Family Medicine Education on Patient Satisfaction

Nataša Pilipović-Broćeta, Gordana Tešanović, Amela Lolić, Jasminka Vučković, Nevena Todorović, Ljubiša Preradović

ABSTRACT

Introduction. The goal of patient satisfaction assessment is to evaluate and improve the quality of health care. This survey aims to assess patient satisfaction with primary health care and to compare satisfaction of patient cared by family physician and those professionals who have not been educated in family medicine.

Methods. In 21 cities of Republic of Srpska, 2146 EuroPep questionnaires have been completed by patients. Total number of questionairres given to the patients was 2200.

Results. Patients gave better score to the family physicians than to physicians who were not educated in family medicine especially to questions related to recovery from disease, emotional problems and doctor-patient contact.

Conclusion. This survey shows benefit of the family medicine education.

Key words: family medicine team, education, EuroPep questionnaire, patient satisfaction

CLINICAL PROBLEM-SOLVING

Bilobectomy for allergic bronchopulmonary aspergillosis mimicking lung cancer

Anthony W. Kim[1]
David D. Lee[2]
Ozuru O. Ukoha[3]
Marin Sekosan[4]

[1]Section of Thoracic Surgery, Yale University, New Haven, CT
[2]Department of Surgery, University of Michigan, Ann Arbor, MI
[3]Division of Cardiothoracic Surgery, John H. Stroger Jr. Hospital of Cook County, Chicago, IL
[4]Department of Pathology, John H. Stroger Jr. Hospital of Cook County, Chicago, IL

Correspondence
Marin Sekosan, M.D.
Chair
Division of Anatomic Pathology
Stroger Hospital of Cook County
1901 W. Harrison Street
Chicago Illinois, 60612
Phone: 312-864-7546
Fax: 312-864-9244

Email: cchmsekosan@yahoo.com

(Scr Med 2011;42:22-5)

Submitted: February 10, 2011
Accepted: March 30, 2011

Allergic Bronchopulmonary Aspergillosis (ABPA) is one of several presentations of pulmonary infections caused by the common fungal organism, *Aspergillus fumigatus*.[1,2] ABPA is characterized by colonization of the respiratory tree with the organism in the absence of tissue invasion and allergic reactions, such as Type I immunoglobulin E (IgE)-mediated hypersensitivity and Type III immunoglobulin G (IgG) immune complex-mediated immune response.[1] This report presents a patient with a pulmonary mass that was resected due to concerns of malignancy but was ultimately found to be an unusual presentation of allergic bronchopulmonary aspergillosis (ABPA).

Case

The patient is a 54-year-old male with a previous medical history significant only for asthma. He recently ceased tobacco use after smoking approximately less than one-half pack per day for several years. He presented to the emergency department with three weeks of pleuritic chest pain associated with coughing. He denied any other symptoms, including fevers, chills, dyspnea, exertional chest pain, or productive sputum. On physical examination, the only significant finding was mild bilateral wheezing. The remainder of his physical examination was normal. His white blood cell count was 6,400/mm^3; however, the differential showed an eosinophilia of 0.9 (13.9%). Additionally, his quantitative IgE antibody count was 1,642ng/ml. On chest radiography he had a solitary nodule in his right upper lobe. A follow-up computed tomography (CT) scan of his chest demonstrated a mass-like consolidation in the anterior segment of the right upper lobe measuring 6.6 x 4.3 cm with patchy areas of consolidation surrounding this area. The consolidation was believed to be post-inflammatory in nature, but an underlying malignancy could not be ruled out. Saccular and central bronchiectasis in the right upper lobe was also noted but was not seen elsewhere in the lungs. (Figure 1)

Flexible bronchoscopy allowed visualization of secretions from the anterior segment bronchus of the right upper lobe (Figure 2). Washings and brushings were negative for malignant cells. Potassium hydroxide (KOH) calcofluor cultures were negative for fungal elements initially and remained negative after six weeks of incubation. The patient was treated with prednisone for over 6 weeks without any change in the size of the mass, as viewed by an interval

chest CT scan, thus raising a concern for malignancy. Accordingly, he was taken to the operating room for thoracotomy.

The tumor crossed the minor fissure from the anterior segment of the right upper lobe, where the bulk of it was located, to the medial segment of the right middle lobe. No other nodules or masses were palpated. Because an incisional biopsy would have been inappropriate in a malignant setting, a right upper and middle bilobectomy was performed.

The patient's postoperative course was uneventful. Gross pathology revealed ill-defined nodules in the right upper and middle lobes on palpation. These areas formed a poorly circumscribed subpleural and intraparenchymal consolidation measuring approximately 2.0 x 2.0 x 2.0 cm. Sections of this area revealed bronchiectasis with mucopurulent material. Mucoid impaction of the bronchi with a large pasty brown plug was noted. Gomori methenamine silver (GMS) staining revealed fungal hyphae in an intrabronchial mucoid plug, but there was no evidence of invasive fungi in the lung parenchyma or bronchial walls. No malignancy was found. (Figure 3)

Discussion

Allergic Bronchopulmonary Aspergillosis (ABPA) classically presents with symptoms and signs of cough, fever, malaise, anorexia, headache, dyspnea, wheezing, respiratory distress, pleuritic chest pain, hemoptysis, and asthma attacks during episodic or recurrent exacerbations.[1,2] Clubbing, crackling, and cor pulmonale may be harbingers of end stage disease associated with long standing fibrosis.[1,2] Pulmonary fibrosis and bronchiectatic changes are believed to develop from inspissated plugs of mucus consisting of *aspergillus* and eosinophils in the segmental and subsegmental bronchi.[2,3] Expectoration of these plugs results in the production of green, beige, or brown colored sputum.[1] During an exacerbation, antigens from proliferating fungi in the airway trigger a type I hypersensitivity reaction with IgE and IgG-mediated release of inflammatory mediators. Necrosis and cellular infiltrates are produced, leaving deposits of immune complexes and inflammatory cells that ultimately cause bronchial wall damage and bronchiectasis.[1]

Eight clinical, radiologic, and serologic criteria have been established to diagnose ABPA: asthma, immediate cutaneous reactivity to *Aspergillus*, precipitating antibodies to *Aspergillus fumigatus,* elevated total serum IgE, peripheral eosinophilia, radiologic pulmonary "infiltrates," proximal bronchiectasis, and elevated levels of serum IgE and IgG compared with those in mold- sensitive asthmatic patients.[1] The findings of eosinophilia in a setting of asthma or cystic fibrosis should raise the specter of this disease entity, although eosinophilia alone is a nonspecific finding.[4] If ABPA is suspected, the initial evaluation should include a skin prick test or intradermal reactivity to aspergillus. If this is positive, then the total IgE precipitins to aspergillus can be measured in serum. Elevation of serum IgE, *i.e.*, greater than 1000 ng/ml, can occur in the asthmatic patient, especially during an ABPA exacerbation. A two-fold elevation of IgE *Aspergillus fumigatus*-specific antibodies are useful for discrimination between asthmatics with and without ABPA.[1] The real value of total serum IgE is as a clinical tool to track its rise and fall during exacerbations and remissions.[1]

Bronchial impaction with mucous is frequently described as a distinct feature of ABPA. In a study by Bosken and colleagues, 11 of 18 patients with ABPA had mucoid impaction of bronchi.[3] ABPA has been described on chest radiograph as a transient pulmonary or mass-like infiltrate. The infiltrative appearance is secondary to active or previous mucoid impaction of the proximal bronchi.[2,4] These mucoid impactions can extend as branching opacities typically in an upper lobe distribution and appear to be associated with central bronchiectasis on plain chest radiography.[2]

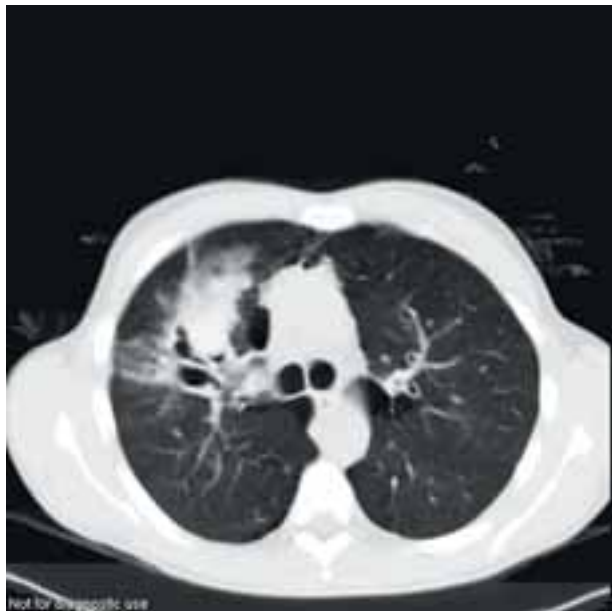


Figure 1. CT scan demonstrating an area of confluence in the anterior segment of the right upper lobe measuring 6.6 x 4.3 cm. Patchy areas of consolidation surrounding an area with central bronchiectasis and encroaching on the fissure.

CT scanning is helpful in further delineating ABPA. Bronchial mucus plugging is commonly a characteristic finding in ABPA[4] and on CT scan, it can exhibit branching while coursing along the bronchial tree, producing a "finger-like projection," "gloved-finger," or "toothpaste shadow" appearance. The presence of a hyperdense mucus plug may be pathognomonic for ABPA in the setting of asthma.[2,4] Central bronchiectasis is also strongly suggestive of this disease process, but may be absent early in its course[4] or present without ABPA in asthmatics.[1]

PET scanning has not been used routinely for the evaluation of patients with ABPA. It was not used in this case because there was a strong suspicion of malignancy, and PET scanning would be unable to distinguish between neoplasm and infection.

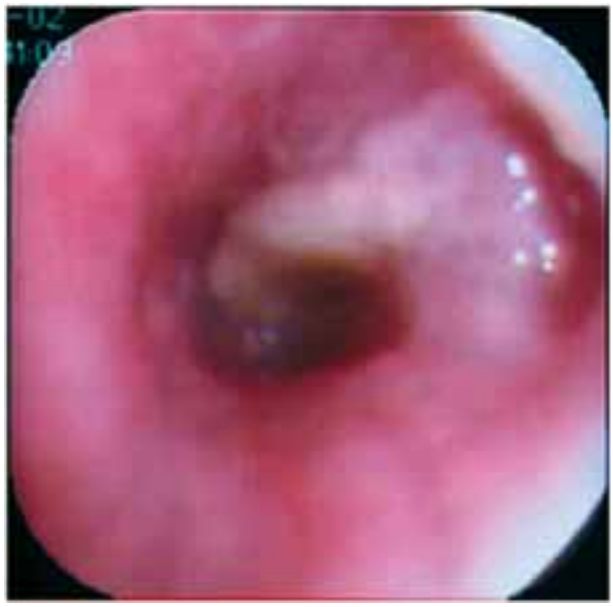


Figure 2. Flexible bronchoscopy revealing minimal secretions form right upper lobe anterior segment bronchus.

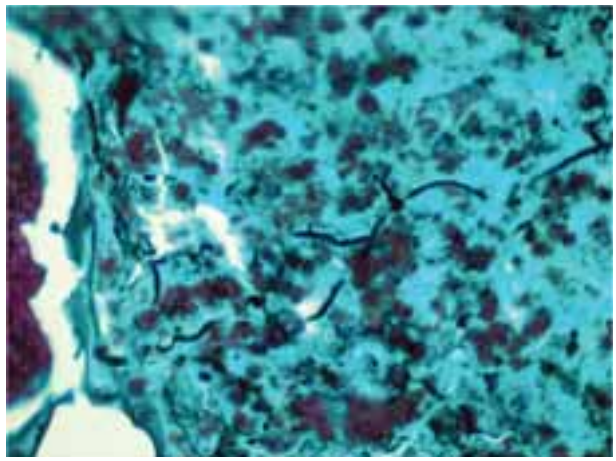


Figure 3. High magnification (450x) of a Gomori Methenamine Silver (GMS) stain slide from an intrabronchial mucoid plug showing rare fungal hyphae morphologically consistent with Aspergillus species.

The presence of ABPA mistaken for a malignancy has been reported.[3,5] Conversely, the growth pattern of some malignancies have the appearance of and have been mistaken for ABPA.[1] In a review of ABPA in non-asthmatics, 8 of 19 patients with abnormal radiograph findings of a pulmonary mass were suspected of harboring cancer.[5] A review of the Western literature indicates that the exact frequency with which ABPA presents as a lung mass is unknown, but it usually is not treated surgically.

Bronchoscopy has been used both in the diagnosis[3-5] and in the treatment through aspiration[4] in patients with mucoid impaction. While it may allow for the aspiration of sputum for culture, cultures of *Aspergillus fumigatus* are not entirely diagnostic and may only provide supportive evidence.[1] Bronchoscopy findings may be used to rule out malignancy, but the cytology results can be misleading.[3,5]

The patient presented in this report was unique in that the aspergillus infection did not respect the anatomic planes of the lobes of the lung and traversed the minor fissure. Ultimately because of concerns that the mass was malignant, the patient required a bilobectomy, which has not been described previously as a treatment for ABPA. A percutaneous biopsy of the lesion was not performed in the patient reported here, because he had a post-obstructive clinical presentation, which is not uncommon for a malignant neoplasm of the lung. Historically, open lung biopsies were performed to aid in the diagnosis of ABPA.[3] Because of accurate laboratory tests and improved imaging techniques as well as an improved clinical acumen, the role of open lung biopsy for a relatively straightforward presentation now has decreased utility. A review of the literature suggests that there is no role for routine image-guided percutaneous biopsy of suspected ABPA lesions.[1] Furthermore, surgical intervention for ABPA is less frequently described; the largest series was reported by Bosken and colleagues. None of their 18 patients underwent a preoperative invasive procedure to arrive at a tissue diagnosis. In particular, five in this cohort did not have enough clinical information to achieve a preoperative diagnosis.[3]

The cornerstone of treatment for ABPA is steroid therapy, which suppresses the immune response. Oral prednisone, slowly tapered over three to six months, is recommended. Clinical responses should be monitored with monthly or bimonthly serum total IgE concentrations. The role of inhaled corticosteroids is undefined. Total serum IgE levels can be monitored to gauge clinical effectiveness along with symptomatic and radiographic improvement.[1] Once total serum IgE levels normalize, the steroid dosages can be tapered.[1] Ultimately, steroid therapy results in the resolution of mucoid impaction and bronchiectasis.[1] The typical rapid resolution of radiographic infiltrates after two to four weeks of therapy should prompt the search for a refractory mucus plug or lung collapse.[1]

While reviews of several studies suggest that antifungal therapy (itraconazole, vorconazole, or other imidazole agents) conveys a modest benefit, its overall usefulness in the treatment of ABPA has yet to be established. Accordingly, unequivocal use of antifungal agents should be limited.[1] They should be administered as an adjunct to corticosteroid therapy rather than in lieu of it.

Indications for surgery include: 1) persistence of a mass despite of maximal medical therapy in patients with strong risk factors for bronchogenic carcinoma, 2) recurrent or persistent escalating hemoptysis, and 3) post-obstructive complications such as, atelectasis, pneumonia, or lung abscess. The presence of bronchiectasis almost invariably requires anatomic resection rather than wedge resection. The patient presented in this report required a bilobectomy because of the persistence of radiologic abnormalities, concerns for malignancy and the extent of his disease.

Acknowledgements

The authors acknowledge Eric Cuasay M.D., from the Swedish American Medical Group, Rockford, Illinois for his radiologic expertise.

No potential conflict of interest relevant to this article was reported.

References

1. Vlahakis NE, Aksamit TR. Diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Mayo Clin Proc* 2001;76(9):930-8.
2. Gotway MB, Dawn SK, Caoili EM, Reddy GP, Araoz A, Webb RW. The radiologic spectrum of pulmonary aspergillus infections. *J Comput Assist Tomogr* 2002;26:2:159-73.
3. Bosken CH, Myers JL, Greenberger PA, Katzenstein ALA. Pathologic features of allergic bronchopulmonary aspergillosis. *Am J Surg Path* 1988;12:216-22.
4. Karunaratne N, Baraket M, Lin S, Ridley L. Thoracic CT illustrating hyperdense bronchial mucous plugging. *Australasian Radiology* 2003;47:336-8.
5. Sanchez-Alarcos JMF, Martinez-Cruz R, Ortega L, Calle M, Rodriguez-Hermosa JL, Alvarez-Sala JL. ABPA mimicking bronchogenic cancer. *Allergy* 2001;56:80-1.

CASE REPORT

Spontaneous Resolution of Spinal Epidural Hematoma

Aleksandra Dominović-Kovačević[1], Tihomir Ilić[2], Sanja Grgić[1], Zoran Vukojević[1], Violeta Kovačević-Dragosavljević[3]

[1]Clinic for Neurology, Clinical Center of Banja Luka, Republic of Srpska, Bosnia and Herzegovina
[2]Clinic for Neurology, Military Medical Academy, Belgrade, Serbia
[3]Center for Radiology,Clinical Centre of Banja Luka
Bosnia and Herzegovina

Correspondence
Aleksandra Dominović-Kovačević, MD
Address: Majke Knežopoljke 3
78000 Banja Luka
Bosnia and Herzegovina
Phone: + 38765301511
E-mail: dominovic@blic.net

(Scr Med 2011;42:26-7)

Submitted: January 10, 2011
Accepted: April 10, 2011

A 48-year-old female (H: 172 cm, W: 67 kg, BMI: 22.6 kg/m2) presented to our neurology clinic with severe pain in the thoracic spine region. This was associated with flaccid paralysis, sensory deficit in the T4-T6 dermatomes, as well as bladder and bowel dysfunction. Her past medical history was unremarkable, and she was not taking any medications. The observed deficits proceeded rapidly, despite the lack of obvious disease in the patient's medical history. On admission, the patient's neurological status was as follows: she was immobile with normal status of the neck and upper extremity as well as the cranial nerves; she had flaccid paralysis with symmetrical absent reflexes in lower-extremity and pathological reflexes indicating abnormalities in the T4-T6 sensory level, with accompanying bladder and bowel dysfunction.

Laboratory tests were normal. The results of coagulation studies, including prothrombin time, partial thromboplastin time, and bleeding time, were normal. Both macroscopic and microscopic urine analyses were normal. Magnetic resonance imaging revealed a left posterior epidural hematoma extending from the second to the third thoracic segment that deformed the spinal cord (Fig. 1). A consulting neurosurgeon suggested surgical decompression.

Following disapearance of the hematoma, the patient's initial symptoms gradually improved within 24 hours of their appearance and during the following day. The patient could now move with assistance. Twelve days later, another MRI showed no abnormalities (Fig. 2). Therapy included mannitol, analgesics, and vitamins. The patient experienced a full spontaneous recovery after twelve days. She became mobile without weakness in lower-extremity, and without bladder or bowel dysfunction.

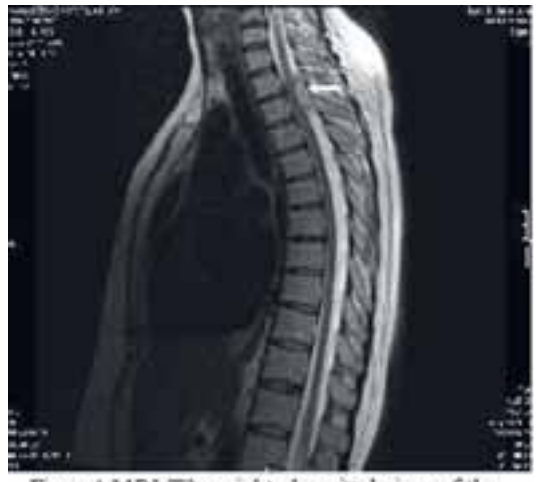


Figure1:MRI-T2-weighted sagittal view of the extradural hematoma extending from T2-T3

Spontaneous spinal epidural hematoma (SSEH) was first reported in 1869 by Jackson,[1] who described the stereotypic

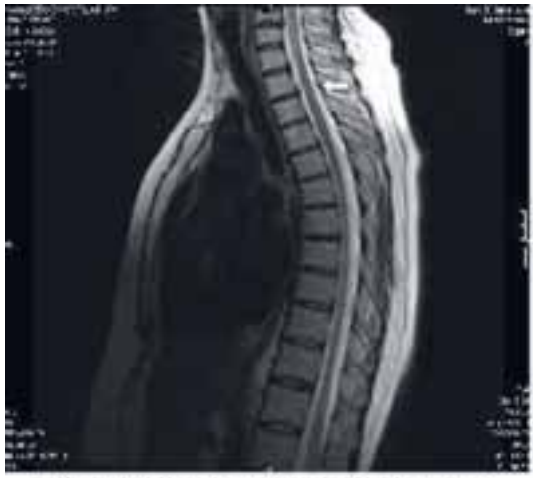


Figure 2: MRI-T2 weighted sagittal after 12 days view resolution epidural hematoma

symptoms in detail: sudden severe spinal pain with radiating pain corresponding to the bleeding spot, followed within a few days by a progressive paralysis in both lower extremities and impairment of bladder and bowel function due to spinal cord compression. Although SSEH is reported to occur in all age groups, it is most frequent after the fourth or fifth decade of life. Some causes of SSEH are related to minor trauma (lumbar puncture, spinal anesthesia); others are spontaneous, but more often SSEH occurs in patients on anticoagulant therapy or those with coagulation abnormalities, individuals with neoplasms at different localization, with vascular malformation, or in those with immune-mediated vasculitis and arterial hypertension.[2] In 40% of cases the cause remains unidentified.[3] Differential diagnosis suggests the possibility of acute transverse myelitis, as well as tumors of the spinal cord.

Spinal MRI is essential for early detection of the location of SSEH as well as its compression status.[2] The hematoma appears isointense on T_1 sequences. In T2 sequences, acute hematomas appear hyperdense at the periphery with a hypodense center. Nonsurgical therapy may be justified when there is minimal neurological deficit, or if there is evidence of early spontaneous resolution of the hematoma.[2] Alexiadou-Rudolf at al.[4] reported that surgery within 12 hours produced favorable functional results in cases that needed early surgical decompression. However, Lawton et al.[5] argued that is very difficult to gauge the optimum time for decompressive surgery. Wagner et al. and Rechtine et al.[3,6] reported spontaneous resolution of SSEH, as we found in this study as well. Multidisciplinary collaboration, continuous monitoring of the patient, as well as hourly monitoring of neurological deficit, allowing a timely decision about surgery, helped us achieve a favorable outcome for our patient.

References

1. Jackson R. Case of spinal apoplexy. Lancet 1869;2:5-6.
2. Groen RJ, Ponssen H. The spontaneous spinal epidural hematoma. A study of The etiology. J Neurol Sci 1990;121-38.
3. Wagner S, Hacke W. Spontaneus resolution of a large spinal epidural hematoma: Case Report, Neurosurgery 1996;38:816-8.
4. Alexiadou-Rudolf C, Emestus RI, Nanassis K, Lanfermann H, Klug N. Acute nontraumatic spinal epidural hematomas. An important differential diagnosis in spinal emergancies. Spine 1998;23:1810-13.
5. Lawton MT, Porter RW, Heiserman JE, Jacobowitz R, Sonntag VK, Dickmen CA. Surgical menagement of spinal epidural hematoma: relationship between surgical timing and neurological outcome. J Neurosurg 1995;83:1-7.
6. Rechtine G, Bolesta MJ, Louis K. Spontaneus resolution of symptomatic post-traumatic cervical epidural hematoma. J Bone Joint Surg Am. 2001;83-A(2):255-8.

CASE REPORT

A Young Woman with a Swollen and Tender Umbilical Nodule

August A. Natalie, Anjeli K. Isaac
Department of Medicine, Division of Dermatology, John H. Stroger, Jr. Hospital of Cook County, Chicago, Illinois 60612, USA

Correspondence
August A. Natalie, MD
John H. Stroger Jr. Hospital of Cook County
Department of Internal Medicine
Division of Dermatology
Chicago, Illinois 60612
USA
Email: anatalie@gmail.com

(Scr Med 2011;42:28-9)

Submitted: April 2, 2011
Accepted: May 5, 2011

A 20-year-old woman presented with a six-month history of a swollen and tender umbilical nodule (**Figure 1A**). The patient reported intermittent pain in that area since age nine. She recalled monthly episodes of umbilical swelling and bleeding, followed by regression. The pain was worse with sitting and at times persisted throughout the day. She also noted recurrent tender subcutaneous nodules in the periumbilical area and within abdominal striae. Menarche began at age ten. She had regular menstrual periods every 23 days, but they were complicated by significant menorrhagia. Review of systems was notable for dyspnea, a sensation of something pushing up on the diaphragm, chronic burning in the lower abdomen, alternating diarrhea and constipation, infertility for the past18 months, and intermittent but severe back pain. An abdominal ultrasound performed by the primary care physician was negative for umbilical hernia. A punch biopsy of the umbilical nodule was obtained (**Figure 1B** and **1C**).

The skin biopsy specimen showed two small isolated atypical glands with ciliated columnar epithelium surrounded by scant stroma. There was no evidence of granulomas, hemorrhage, hemosiderin or fecal material. A diagnosis of cutaneous endosalpingiosis was made. The patient was offered excision of the umbilical nodule, but she opted to try medical management first. She was referred to the gynecology-endocrinology department for evaluation and was started on leuprolide, a gonadotropin-releasing hormone (GnRH) agonist.

Endosalpingiosis is the aberrant growth of Fallopian tube epithelium outside of its usual location.[1] Endometriosis and endosalpingiosis are similar disease entities that share common clinical features. There is a paucity of information regarding endosalpingiosis in the literature; thus, the management of endosalpingiosis derives from the literature on endometriosis. Endometriosis (ectopic endometrial tissue) is an estrogen-dependent inflammatory disease that affects 5% to 10% of women of reproductive age in the United States.[2] The main clinical features of endometriosis are pelvic pain, dysmenorrhea, dyspareunia, cyclical bowel or bladder symptoms and infertility.[3] It is well known that endometriosis can produce skin lesions, with a predilection for abdominal scars[3] and the umbilicus.[4] The incidence of cutaneous endometriosis is between 1.1%[3] and 5.2%.[5] Endometriosis of the umbilicus (also known as a Villar's nodule) is a rare clinical finding with an estimated incidence of 0.5% to 1% of all patients with endometrial ectopia.[6]

Umbilical endometriosis usually follows laparoscopic surgery; however, spontaneous lesions have been reported as well.[4] Umbilical endosalpingiosis appears to be an even rarer disease. To our knowledge, only four cases of cutaneous endosalpingiosis of the umbilicus have been reported.[1, 7, 8] An umbilical nodule requires biopsy in order to rule out the possibility of malignant melanoma or a Sister Mary Joseph nodule (metastasis usually from an intra-abdominal tumor).

There are three different theories concerning the pathogenesis of endosalpingiosis. These are similar to the pathogenesis of endometriosis: metaplasia, implantation and metastasis.[1] According to the metaplasia theory, the peritoneum retains the potential for differentiation into various types of epithelium, including endometrial tissue. The implantation theory suggests that retrograde passage

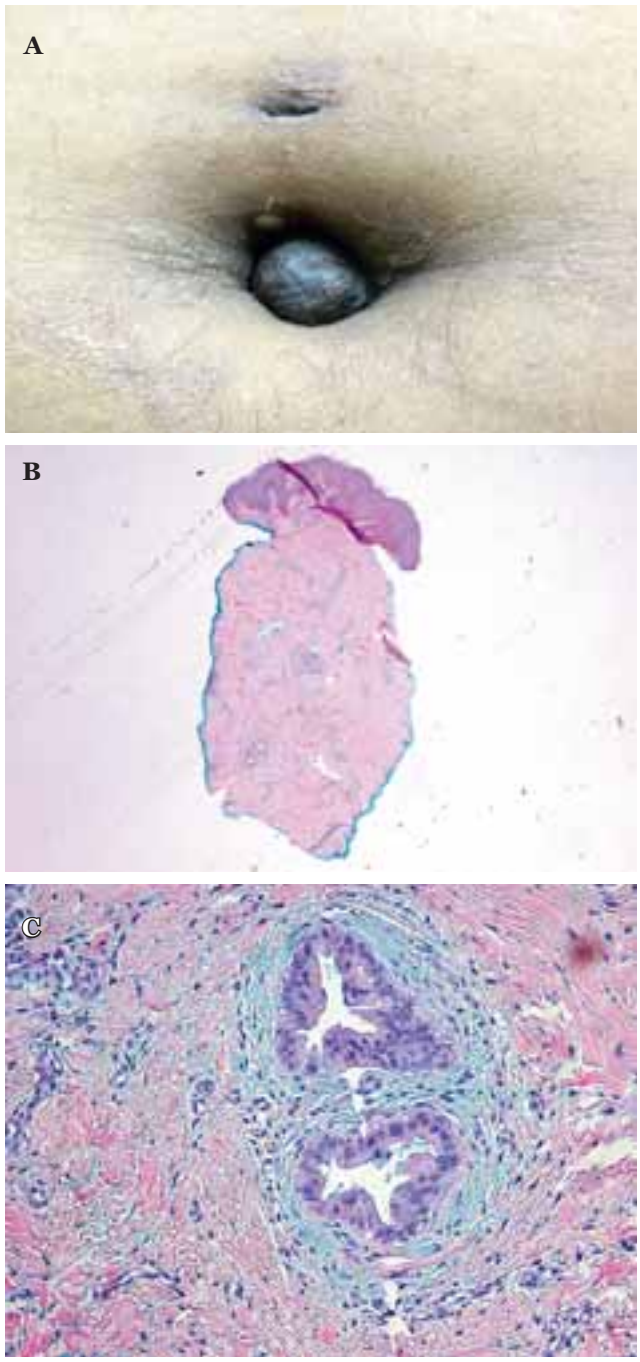


Figure 1. Umbilical nodule. A. Umbilical swelling, B. A punch biopsy of the umlical nodule, C. Skin biopsy-tvo small isolated atypical glands.

of tubal tissue during menstruation can implant on pelvic structures. Finally, the metastatic theory suggests that salpingeal tissue spreads via vascular or lymphatic vessels.

The mainstays of treatment for endometriosis are medication and/or surgery, depending on whether therapy is being directed toward pelvic pain or infertility.[9] Both medical and surgical treatments are effective for treatment of pelvic pain. Therapeutic options include NSAIDs, oral contraceptives, or GnRH-agonist therapy, and if these prove unsuccessful, laparoscopy. For infertility associated with endometriosis, medical treatment is ineffective, but surgical removal of endometrial tissue is beneficial for most women.

Our patient received seven injections of leuprolide 3.75mg IM monthly. After two injections, she noted cessation of the umbilical bleeding. Eight months after beginning leuprolide, she underwent a diagnostic laparoscopy with chromopertubation that revealed a normal uterus and ovaries; the fallopian tubes were open with normal flow of methylene blue from the fimbriae. Four months later, umbilical bleeding and painful menstrual periods resumed. She has been since referred to general surgery for umbilical tissue removal.

REFERENCES

1. Dore N, Landry M, Cadotte M, et al. Cutaneous Endosalpingiosis. *Arch Dermatol* 1980;116:909-12.
2. Bulun SE. Endometriosis. *N Engl J Med* 2009;360:268-79.
3. Agarwal A, Fong YF. Cutaneous endometriosis. *Singapore Med J* 2008;49:704-9.
4. Chatzikokkinou P, Thorfinn J, Angelidis IK, et al. Spontaneous endometriosis in an umbilical skin lesion. *Acta Dermatovenerol Alp Panonica Adriat* 2009;18:126-30.
5. Douglas C, Rotimi O. Extragenital endometriosis--a clinicopathological review of a Glasgow hospital experience with case illustrations. *J Obstet Gynaecol* 2004;24:804-8.
6. Dessy LA, Buccheri EM, Chiummariello S, et al. Umbilical endometriosis, our experience. *In Vivo* 2008;22:811-5.
7. Perera GK, Watson KM, Salisbury J, et al. Two cases of cutaneous umbilical endosalpingiosis. *Br J Dermatol* 2004;151:924-5.
8. Redondo P, Idoate M, Corella C. Cutaneous umbilical endosalpingiosis with severe abdominal pain. *J Eur Acad Dermatol Venereol* 2001;15:179-80.
9. Olive DL, Pritts EA. Treatment of endometriosis. *N Engl J Med* 2001;345:266-75.

IMAGES IN CLINICAL MEDICINE

Giant Ovarian Cyst in Sixteen-Year-Old Girl

Mirko Raković, Zoran Rakonjac, Mirko Šatara, Miroslav Popović

Department of Pediatic Surgery
Medical Faculty
University of Banja Luka
78000 Banja Luka,
Republic of Srpska
Bosnia and Herzegovina

Correspondence
Dr Mirko Raković
Email: mirkos@teol.net

(Scr Med 2011;42:30)

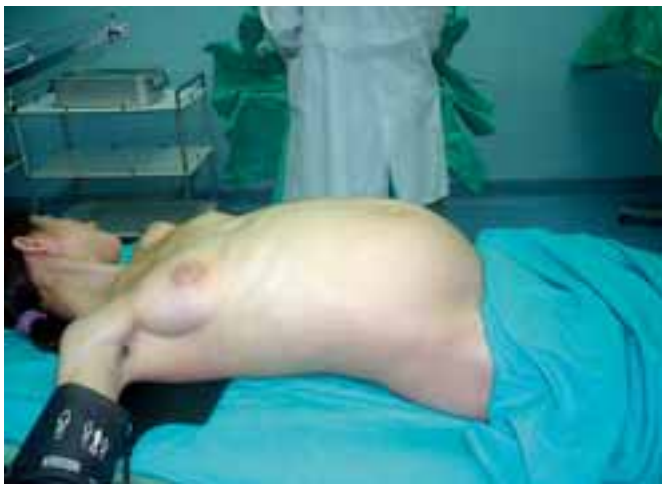


Figure 1. Abdominal appearance before laparascopy

A 16-year-old girl was admitted to the Department of Child Surgery with an asymptomatic lump in her abdomen. Ten months before, she had noticed that "her belly grows", and during a few months before admission, her abdomen began to grow faster. Physical examination showed an enlarged abdomen (Figure 1). The abdominal wall was tense, and palpation and percussion indicated a large abdominal mass. Computerized tomography and ultrasound examination confirmed the mesenteric or ovarian localization of the cyst and demonstrated almost total displacement of the surrounding structures. Laparoscopy was contraindicated because of the size of the cyst, which limited the working space and posed a high risk of spillage.[1] Instead, laparotomy was done, revealing a huge cyst in the left ovary that pushed the surrounding structures to the periphery. The cyst (35.6 cm x 14, 9 cm) was surgically removed. It contained 10.5 L of serous liquid. The size puts it among the largest ovary cysts that have been described in adolescents. Indications for surgical treatment of ovarian cysts include all symptomatic cysts and any larger than 5 cm.[2] In our case, a safe, total cystectomy was done, because the cyst was located in the pelvis minor with limited approach to laparoscopy, and because we could not rule out a malignant genesis.

References

1. Mayer JP, Bettolli M, Kolberg-Schwerdt A, Lempe M, Schlesinger F, Hayek I, Schaarschmidt K. Laparoscopic approach to ovarian mass in children and adolescents: already a standard in therapy. J Laproendosc Adv Surg Tech A 2009:19:S111-5.
2. Goh SM, Yam J, Loh SF, Wong A. Minimal access approach to the management of large ovarian cysts. Surg Endosc 2007; 21: 80-83.

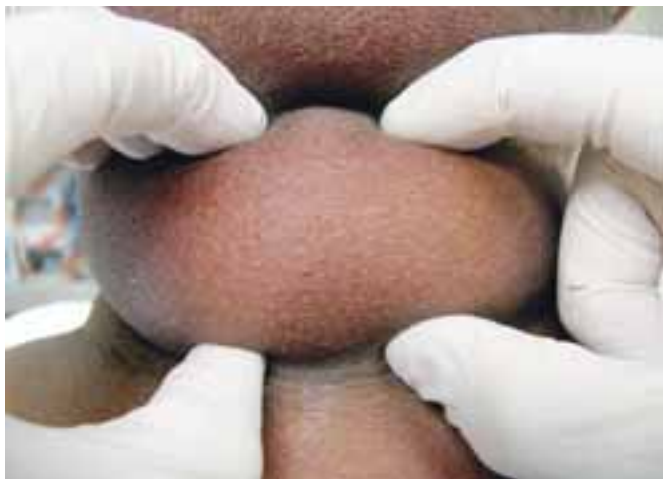
IMAGES IN CLINICAL MEDICINE

Type 3 Scleredema

August A. Natalie
Stroger Hospital of Cook County
Department of Internal Medicine
Division of Dermatology
Chicago, Illinois 60612
USA

Correspondence
August A. Natalie, MD
Stroger Hospital of Cook County
Division of Dermatology
Chicago, Illinois 60612
USA
Email: anatalie@gmail.com

(Scr Med 2011;42:31)



A 55-year-old male with type 2 diabetes mellitus, last glycated hemoglobin (A1c) 11.80, was referred to the dermatology clinic with a posterior neck mass. The primary care physician performed a CT scan of the neck, which revealed a prominence of subcutaneous fat, but no identifiable mass. Serum protein electrophoresis showed no obvious M-spike. Additionally, an incisional wedge biopsy of the posterior neck revealed no evidence of an underlying lipoma. Instead, the histopathology included a markedly thickened dermis extending past the sweat gland coils, and there were thick collagen bundles separated by clefts. Colloidal iron staining showed increased mucin deposition between the collagen bundles, supporting a diagnosis of type 3 scleredema.

Comment. Skin manifestations of diabetes mellitus occur in approximately 30% of patients during the course of their illness.[1] One such manifestation is scleredema, also known as scleredema adultorum and scleredema diabeticorum of Buschke. This condition is characterized by a diffuse, symmetric, non-pitting induration of the skin that usually involves the upper back, shoulders, and neck. The onset of scleredema is insidious, and it is usually found incidentally by the examining physician.[2] Major consequences of this disease include decreased mobility of the shoulders, impairment of respiratory function, sleep apnea, and monoclonal gammapthy.[3] It is believed the skin changes are caused by deposition of glycosaminoglycan within the dermal connective tissue. On histological examination, the reticular dermis is obviously thickened with mucin deposition between the thickened collagen bundles.

There are three types of scleredema adultorum. Type 1 is usually proceeded by a febrile episode (commonly caused by Streptococcal infections), type 2 involves developing paraproteinemias, including multiple myeloma, and type 3 is associated with diabetes mellitus.

The prevalence of scleredema in adult diabetic patients has been only minimally examined. The largest prospective study to date, consisting of 484 diabetic outpatients, reported a prevalence of 2.5%.[4]

Scleredema may be associated with both type 1 and type 2 diabetes mellitus.[3] Risk factors for development of scleredema in conjunction with diabetes include: long duration of diabetes, the presence of microangiopathy, being overweight, the need for insulin, and presence of albuminuria.[3] It is generally felt that glycemic control does not affect the condition.

References

1. Ahmed I, Goldstein B. Diabetes mellitus. Clin Dermatol 2006;24:237-46.
2. Venencie PY, Powell FC, Su WP, et al. Scleredema: a review of thirty-three cases. J Am Acad Dermatol 1984;11:128-34.
3. Meguerditchian C, Jacquet P, Beliard S, et al. Scleredema adultorum of Buschke: an under recognized skin complication of diabetes. Diabetes Metab 2006;32(5 Pt 1):481-4.
4. Cole GW, Headley J, Skowsky R. Scleredema diabeticorum: a common and distinct cutaneous manifestation of diabetes mellitus. Diabetes Care. 1983;6:189-92.

IMAGES IN CLINICAL MEDICINE

A Thirty Nine-Year-Old Woman with an Abdominal Mass

(Scr Med 2011;42:32)

Mark Podberezin
Department of Pathology
University of Illinois at Chicago and
Stroger Hospital of Cook County
Chicago, IL 60612, USA

Correspondence
Mark Podberezin, MD
Department of Pathology
University of Illinois at Chicago
Chicago, IL 60612, USA

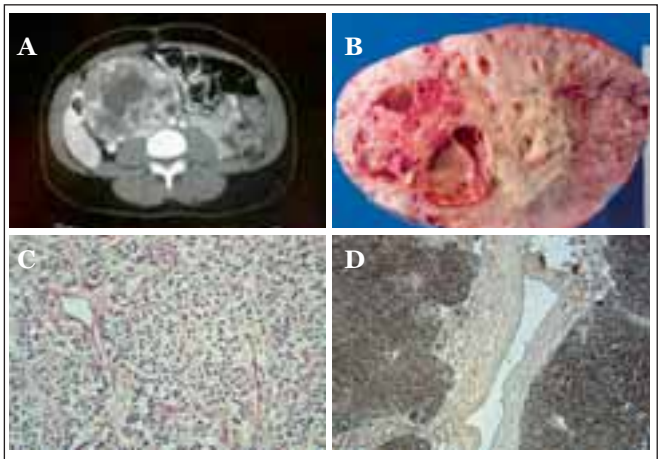


Figure 1. Abdominal Mass. A. Disorganized vessels, cystic and necrotic material, B. Areas of necrosis, C. Sheets and clusters arrangments of the cells, D. Chromograin positive staining.

A 39-year-old African American female, with a history of seizures, schizophrenia, and bipolar disorder, complained of abdominal pain. A CT scan of the abdomen revealed a 12 cm complex mass in the right side of the mid abdomen. The mass was located retroperitoneally and showed heterogeneity, with disorganized vessels, as well as cystic and necrotic material (Figure 1A). The lesion extended superiorly to the gallbladder and inferiorly to the ileocecal junction and appendix. Normal structures of the abdomen were compressed by the adjacent mass, but there was no evidence of invasion. Based on the radiologic features, differential diagnosis included benign necrotic mesenchymal tumor (leiomyoma or stromal tumor) or leimyosarcoma. Primary pancreatic or gynecological tumors were less likely possibilities.

The mass was completely resected. On the gross examination, it was 17.1 x 12.7 x 6.7 cm in size and well-encapsulated. The cut surface showed areas of necrosis, friable tissue and cystic areas (Figure 1B)

Histologic examination of the mass showed proliferation of monotonous cells with round nuclei and moderate amounts of cytoplasm. These cells were arranged in small sheets and clusters (Figure 1C). There was little cellular atypia, and mitotic figures were seen only rarely. Immunohistochemical stains showed that the lesion was positive for chromogranin (Figure 1D), synaptophysin, and CD117. Additional stains for CD34, S100, smooth muscle actin, desmin, and keratin AE1/AE3 were all negative. Based on microscopic and immunohistochemical features, a diagnosis of paraganglioma was made. The patient did not need any additional treatment after surgical removal of the mass.

Comment. In some cases, differential diagnosis of paragtanglioma includes gastrointestinal stromal tumor (GIST) and gastrointestinal autonomic nerve tumor (GANT). GIST are characterized by immunopositivity for CD117/c-kit and CD34, while paraganglioma cells do not express the above markers. GANT is considered to be an ultrastructural subtype of GIST which, in 20% of cases, is characterized by positivity of tumor cells for S100, while the vast majority of GIST cases are S100-negative. In addition, diagnosing GANT requires use of electron microscopy (EM). In GANT, EM reveals presence of complex interdigitating cell processes with bulbous synaptic terminals, small, dense core neurosecretory granules (uniform, 190 nm, submembrane spaces), rudimentary cell junctions, intermediate filaments. In our case, the morphologic “zellballen” pattern, as well as strong and diffuse immunopositivity for neuroendocrine markers was consistent with diagnosis of paraganglioma.

LETTERS TO THE EDITOR

Tissue Engineering and Regenerative Surgery

To the Editor: I read the article entitled "Engineering human tissue" by G. Vunjak-Novaković published in the last issue of this journal.[1] I found this paper very complete and informative for the readers having very different backgrounds.

Tissue engineering as well as cell engineering represents a basis of "new medicine" that has just opened a brand new, *regenerative* stage of surgery. Surgery initially was strictly *ablative* (limited to removing the diseased body-part), then it became *reconstructive & reparative*, and after that this medical discipline entered the stage of organ *replacement* (but transplantation of organs or tissues is limited due to a severe shortage of donors).[2] Thanks to the recent advances in tissue and cell engineering that mark the beginning of the 21st century, *regenerative* surgery may soon offer novel therapies for patients with injuries, end-stage organ failure, or other clinical problems, and become medicine's greatest gift to humanity.[3,4]

Unfortunately, the majority of clinicians are more and more specialized and "formatted" by the guidelines and less and less educated in general and cellular biology. Thus papers like this one[1] are necessary to inform the community of practitioners about the possibilities offered by research and development in this field of medicine that may be soon marked as therapeutic revolution.[5]

In future, I would welcome more papers of this kind in the *Scripta Medica*.

Zoran Ivanović, MD, PhD, HDR
Scientific Director
Aquitaine-Limousin Branch of French Blood Institute
Bordeaux, France

References

1. Vunjak-Novakovic G. Engineering human tissue. Scripta Medica 2010;41:83-7.
2. Gonzales-Crussi F. A short history of medicine. New York, A Modern Library Chronicles Book, 2007.
3. Wong VW, Rustad KC, Longaker MT, Gurtner GC. Tissue engineering in plastic surgery: a review. Plast Reconstr Surg 2010;126:858-68.
4. Atala A. Engineering organs. Curr Opin Biotechnol 2009;20:575-92.
5. Polykandriotis E, Popescu LM, Horch RE. Regenerative medicine: then and now-an update of recent history into future possibilities. J Cell Mol Med 2010;14:2350-8.

Handicapped Students and Admission to Medical Schools

To the Editor: I read with great interest the two articles published on the life and achievements of two prominent scientists, Arthur Guyton and Alon P. Winnie[1,2]. Professor Guyton is well known for his physiology textbook that is still used by medical students all over the world, and his scientific contributions to physiology. Dr. Winnie is known to every anesthesiologist for his contributions to regional anesthesia and for his books on this topic. Both men were stricken with poliomyelitis during their residency. Even confined to wheelchairs, each succeeded in becoming a leader.

After reading these articles, I recalled that one of the medical schools in Bosnia and Herzegovina had a discussion about whether a handicapped student could enter medical school. A student passed the required tests, but his physician stated that the candidate was not physically fit to be a medical doctor because of a missing middle finger. Yet in 1912, Jacob Bolotin[3] became the first person blind from birth to become a physician. He graduated from the medical school in Chicago and became a recognized lung and heart specialist in that city. There have been other, more current cases of visually impaired doctors earning a license to practice medicine. For example, a visually impaired endocrinologist in Windsor successfully practices medicine.

What is the deciding factor as to whether someone can practice medicine? Imagine all the discoveries missed by not allowing handicapped students to study medicine. The majority of them are highly motivated to succeed in our profession. Hopefully these two articles will help the medical community to change their perspective on admissions to medical school.

Biljana Bašić-Panić, MD
Research Office
2425 Tecumseh Road East
Suite 102-2
Windsor, ON, N8W 1E6
Canada
bbasicpanic@yahoo.ca

References

1. Hell JE et al. Athur C. Guyton. *Scripta Medica* 2010;41:15-6.
2. Franco CD. Alon P. Winnie. *Scripta Medica* 2010;41:17-8.
3. Perlman R. *The blind doctor: The Jacob Bolotin story*. Santa Barbara, Blue Point Books, 2008.

LETTER TO THE EDITOR

Fulminant Burning Mouth Syndrome

To the Editor: A 30-year-old-Asian male, a nonsmoker, presented with such severe oral pain that he hardly could speak. The pain had started three days ago in the right lower half of the tongue, and it soon involved the entire tongue and extended to the right ear. The onset of a scalding type of pain was spontaneous with no identifiable precipitating factor. The pain was constant, lasting throughout the day, and the patient complained that it caused loss of sleep during the night. He reported no fever or redness, only a persistent bitter taste. He could not eat or swallow because of the intense pain; consequently, he had great difficulty drinking fluids.

An intra-oral exam showed a normal but slightly dry mucosa and no dental problems. We found no oral lesions or other local pathologies to account for his complaint. Fungal cultures of saliva proved to be negative. The physical exam and laboratory evaluations of this individual were normal. He was normotensive and afebrile. His past medical history was unremarkable. The clinical evaluation and laboratory results led us to make a diagnosis of fulminant burning mouth syndrome.

We referred the patient to the ENT clinic at the University the same day. An examination at the clinic revealed no signs of redness, swelling or other signs of inflammation within the oral cavity, tonsils, and larynx. The ENT consult confirmed our diagnosis of acute burning mouth syndrome. We then initiated treatment with oral gabapentin according to the following protocol: 300 mg on day one; 300 mg twice a day on day two; then 300 mg 3 times a day thereafter. The pain ceased during the second day of medication, and the patient decided to stop taking gabapentin. The pain has not reappeared during a follow up period of two months.

Burning Mouth Syndrome is a chronic pain disorder characterized by burning pain in the absence of mucosal or skin lesions, dysgeusia and xerostomia. There are two clinical forms of this syndrome: primary or essential, and secondary, which results from a local or systemic pathological condition.[1] The therapeutic approach to the secondary form depends on identified etiologies, while the primary form has been successfully treated with gabapentin alone or in combination with alpha lipoic acid.[2] Gabapentin is an analog of GABA that does not react with GABA receptors, but it is thought to block voltage-dependent calcium channels.[3] It is well known that gabapentin alleviates diabetic and other types of neuropathic pain. The abrupt cessation of pain in our patient after only two days might have been a spontaneous event unrelated to the medication, because the therapeutic efficacy of gabapentin generally requires several days.

We report our observations to help physicians and dentists recognize the rare fulminant burning mouth syndrome. In addition, we hope to stimulate further study of the effectiveness of gabapentin treatment for this condition.

Nishit Pancholi, MD, Jilpa Patel, MD
627 S. Wood St. 6th Floor
Chicago, IL 60612, USA.
drnishitpancholi@yahoo.com

References

1. Scala A, Checchi L, Montevecchi M, et al. Update on Burning Mouth Syndrome: Overview and patient management. Crit Rev Oral Biol Med. 2003; 14: 275-91.
2. Lopez-D'alessandro E, Eskovich L. Combination of alpha lipoic acid and gabapentin, it's efficacy in the treatment of Burning Mouth Syndrome: A randomize, double-blind, placebo controlled trial. Med Oral Patol Oral Cir Bucal. 2010; Epub ahead of print.
3. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyaslgia in adults. Cochrane Database Syst Rev. 2011; 3: CD007938.

HISTORIC PERSPECTIVE

Antismoking movement remains alive three decades later

Miroslav Jerinić
Regional hospital Liberec, Husova 59
460 01, Liberec 1
Czech Republic

Correspondence
Miroslav Jerinić, MD
miroslav.jerinic@nemlib.cz

(Scr Med 2011;42:35-6)

Submitted: May 20, 2011
Accepted: May 20, 2011

Medical students in the former Yugoslavia started a national campaign against smoking more than three decades ago. This antismoking movement was successfull until 1992, when war split the country. The medical student campaign, January 31st—A Day Without a Cigarette, was recognized by the World Health Organization (WHO) as one of "the most successful preventive achievements of medical students in Europe." A group of students and professors led by Professor Rajko Igic, the initiator and organizer of this campaign, were guests at the WHO meeting in Geneva, Switzerland (Figure 1). Once the campaign was established nationally and internationally, the Yugoslav government released a postal stamp on January 31st, 1990 (Figure 2).

Figure 1. Group of medical students and professors from Tuzla in Geneva, 1991

Figure 2. Postal stamp issued on January 31st, 1990

The purpose of this short presentation is to remind medical students that they can achieve similar preventive measures. People trust these young medical professionals, because they tend to use innovative approaches for preservation of health. From 1988 to 1990, I was the president of the Antismoking Section at the Medical School, University of Tuzla or *Sekcija za borbu proitiv pusenja medju omladinom* that included more than 80 students. Although I fled the country during the war, I preserved a number of items from that period, including photographs, posters, fliers, the book, *Smoking and Health* (in Serbocroatian and Russian) the postal stamp, letters from former smokers, and several other documents.

Each year, about three weeks before January 31st, we mailed posters (Figures 3-5) to all post offices in the former Yugoslavia for public posting, and we also mailed the posters to all TV and radio stations, daily newspapers and weekly journals in the country. Then, a week before the Antismoking Day, we held a conference for journalists in Belgrade in which we present smoking as a risk factor, discuss smoking cessation and explain how we can prevent young persons to start smoking. On January 31st, students from Tuzla visited Ljubljana, Zagreb, Novi Sad, Belgrade, Sarajevo, Skopje, and several other cities where they participated, along with local students, in radio and TV programs devoted to reduction of smoking. Medical students visited local high schools and talked with students and teachers about specific health problems, including smoking. TV Sarajevo ran, free of charge, short messages such as this: "Children, try to help your parents to quit smoking; they will live longer!" These activities were especially useful during the winter when passive smoking at home and in other closed spaces posed a risk for both children and adults.

The war in Bosnia, UN sanctions imposed to Serbia, and the NATO bombing campaign of the F.R. Yugoslavia (Serbia & Montenegro) weakened the ongoing antismoking

Figure 3. Poster inviting smokers to stop smoking on January 31st. Every year the students printed 10,000 copies and distributed them all over the country.

Figure 4. Medical students at the University of Szeged, Hungary, modified our poster to implore smokers not to smoke for an entire year. Medical students in Tuzla published several thousands of such posters and distributed them within Yugoslavia.

Figure 5. One of several antismoking posters that students in Tuzla printed using drawings from students in the primary school at Buje, Istria, Republic of Croatia.

campaign (1). During this traumatic period, more citizens than ever before, including children and adolescents, started to smoke. However, soon after this time of war, January 31st was again proclaimed as National Antismoking Day in Serbia and the Republic of Srpska. The Republic of Slovenia, and to a lesser extent the rest of Bosnia (the Bosnian Federation), continued to observe this antismoking campaign.

In addition to the National antismoking day, the Republic of Srpska also observes the international antismoking day (May 31st) established by the WHO. The Ministry of Health of the Republic of Srpska encourages all health professionals, medical students, teachers and journalists to participate in both campaigns as well as other smoking cessation activities. This effort appears to be successful. Medical professionals in the Republic of Srpska actively seek new ways to help smokers to quit smoking and to maintain abstinence. In addition to education and professional advice, they often use smoking cessation interventions. Anesthesiologists and surgeons are evaluating how to apply their influence on smokers that require elective surgery.

I would like to suggest that all medical students participate in both national and international antismoking campaigns. They should be included as well in comprehensive smoking intervention programs to improve their smoking cessation counseling skills. Local governments should rigorously enforce laws against smoking in public places, schools, hospitals, and other enclosed spaces (2). Such measures are needed especially in developing countries, because smoking constitutes an even greater risk factor for premature death than hypertension. Newly developed medications to help smoking cessation are still another important tool in the armamentarium of medical doctors.

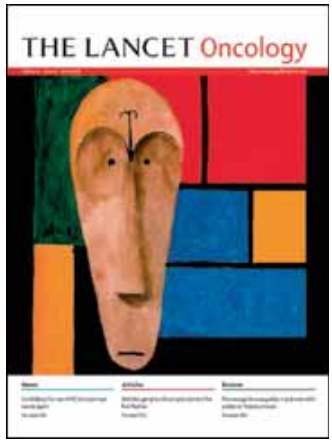
When people from the Balkans and other developing countries come to the USA, where there are strict rules against smoking in many places, they quickly lose their smoking habit. This shows that acculturation can be an important factor. Thus, societal control of smoking should be considered along with voluntary measures in any antismoking program.

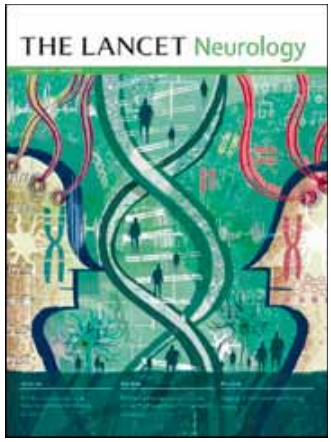
References

1. Sokolova-Djokic, Zizic-Borjanovic S, Igic R. Cigarette smoking in Serbia. Impact of the 78-day NATO bombing campaign. J BUON 2008;13:285-9.
2. Zizic-Borjanovic S, Jerinic M, Igic R. Twenty five years of antismoking movement started by medical students: some further goals. J BUON 2007;12:181-4.

Presentation of Medical Journals and HistCite Software

The Lancet





The Lancet, published since 1823, is as one of the oldest and most respected weekly general medical journals. As an authoritative voice in global medicine, it advances and illuminates medical science and practice worldwide. In addition to clinical medicine, the journal has a strong interest in global public health and international health policy.

The Lancet has, since 1991, been a proprietary title of the publishing house Reed Elsevier. As such, the journal provides an independent voice that is free of influence from pharmaceutical or governmental organizations.

The Lancet's editorial offices are located in London, New York and Beijing. Three weekly editorials convey the opinions and personality of the journal and its editors. Fast-track research articles disseminate clinical and public health data of high global priority and relevance. World Report pieces communicate educational international news stories. Commentaries and Correspondence provide a forum for discussion of material published in *The Lancet* and elsewhere. Reviews and Seminars include commissioned articles that provide state-of-the-art disease-oriented overviews. This substantial jump in thinking leads to testable hypotheses and new understanding of particular problems. The section on *Viewpoints* includes opinion pieces that vary by topic and scope of coverage.

In addition to this landmark weekly journal, three monthly specialty titles featuring original research, as well as review articles, are published under the same label: *The Lancet Neurology*, *The Lancet Oncology* and *The Lancet Infection Diseases*.

Maja Zečević, PhD, MPH
North American Senior Editor
The Lancet
360 Park Avenue South
New York, NY 10016
+1 212 633 3667
m.zecevic@lancet.com

Journal of the Balkan Union of Oncology

The Journal of the Balkan Union of Oncology (J BUON) was founded in 1995, during a period of transition for many countries of the Balkan peninsula that included notorious social reforms, political instability, even wars.

Despite this agitated and confusing situation, a group of doctors from Southeastern Europe decided to show that Medicine knows no borders and that it is, or should be, above hostilities, nationalism and all those ideas and actions that divide people in the end. The establishment of J BUON has proven that this action was not only feasible but also potentially unifying.

J BUON cut rapidly across regional borders to become a truly international Journal. The composition of its editorial staff, the articles published, and its readership come from around the world.

J BUON is published quarterly in Athens, Greece, and it is included in the most important international biomedical databases. It has gained a significant following within a relatively short time. Articles published in this journal deal with clinical and experimental oncology, basic research, as well as the socioeconomic and psychological impact of cancer. There are also reviews of particularly hot topics.

With the dedicated work of all colleagues of the editorial board and staff we are certain that J BUON will become an even better way for authors to make their oncology-related experience and research broadly known, something we believe will work for the benefit of our patients.

Athanasios Athanasiou
Editor-in-Chief
J BUON

Srpski arhiv za celokupno lekarstvo

(Serbian Archives of Medicine)

Srpski arhiv za celokupno lekarstvo / Serbian Archives of Medicine (ISSN 0370-8179) is the Journal of the Serbian Medical Society that was founded in 1872. It publishes articles from medicine and dentistry written by the members of the Serbian Medical Society, by subscribers, and by members of other medical associations and related fields. It is the oldest medical journal in the Balkans (the first issue was printed in August 1874). It is one of very rare medical journals printed in the second half of the 19th century in Europe, and it is also the first scientific journal to be printed using the Cyrillic alphabet.

The Journal publishes original articles, communications, case reports, review articles, articles for practitioners, and articles on history and the language of medicine; it also covers reports from congress and scientific meetings, book reviews, an *In memoriam* column, as well as letters to the Editorial Board. Articles are published *in extenso* in Serbian or English language with abstracts provided in both languages. Articles submitted for publication in the Journal undergo a double-blind review. Reviewers are selected from the most eminent authorities in specific medical fields to evaluate each article submitted to the Journal.

The Editorial Board is composed of 40 medical and dental experts from Serbia and 17 from other countries. The Editor-in-Chief is Mirjana Lapčević, M.D. The Journal is published in six double issues a year; supplements are published as special topic issues.

This general medical journal is included in the Index Medicus database (Medline, PubMed), Journal Citation Reports/Science Edition, Science Citation Index Expanded (Thomson Reuters) and CrossRef (via DOI Serbia). It is also linked to the Internet site www.srp-arh.rs, where all articles published over the last several years are available as full-text and free-of-charge. Yearly grants from the Ministry of Science and Technological Development and the Ministry of Health of the Republic of Serbia support publication of the Journal.

Isidora Ilić i Tatjana Paunović

Pedijatrija Danas

(Paediatrics Today)

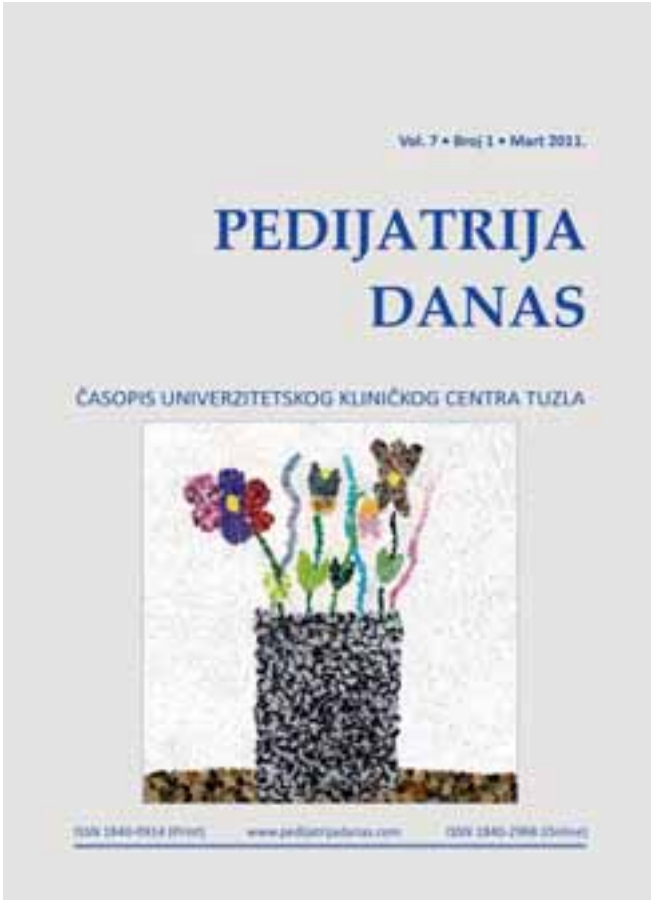
Pedijatrija Danas (Engl. *Paediatrics Today*) is the first paediatrics journal in Bosnia and Herzegovina. It is dedicated to reporting new insights from paediatrics and related areas and to making this information available not only to doctors involved in treating children and adolescents in Bosnia and Herzegovina, but also to doctors in the wider area. The journal publishes articles that are primarily useful in everyday paediatric practice. An electronic version of the journal was launched in 2007, providing reports in both Bosnian and English. *Paediatrics Today* (PT) is published twice a year, and since 2010 two supplements have been printed regularly.

The journal publishes reviewed articles from all areas of paediatrics, including medical genetics, preventive and social paediatrics, and paediatric psychology. In addition, each issue of PT contains a letter from the editor, reviews of books and various news items from the field of paediatric and adolescent medicine. As part of the function of the journal, it also reports on professional meetings for paediatricians. Such meetings have been held twice a year since 2005 in the region of North-East Bosnia. Prominent paediatricians from the area of the former Yugoslavia give lectures that are published, after review, in regular editions of the journal; since 2010 they are published in journal supplements.

Copies of PT are distributed free of charge to national libraries and libraries of medical educational establishments throughout the former Yugoslavia. An exchange has been established with 12 journals from this country and abroad. The journal *Paediatrics Today* is indexed in the *British Library Inside Service*, *Index Copernicus, CAB Abstract/ Global Health databases* and the *EBSCO Publishing Base Academic Search Complete*. Its impact, according to the *Index Copernicus* base, was 5.03 in 2010.

Recently the journal gained a strong reputation not only in Bosnia and Herzegovina, but also in its neighbouring countries, as confirmed by the increasing number of articles and subscribers from the region.

Husref Tahirović
Editor-in-Chief



HistCite Software

Zdravko Grubač[1], Soren Paris[2]

[1]Banja Luka, Republic of Srpska
Bosnia & Herzegovina
[2]Thompson Peuters
Philadelphia, Pennsylvania
USA

Correspondence
e-mail: zd.grubac@gmail.com
e-mail: Soren.Paris@thompson-reuters.com

(Scr Med 2011;42:42-4)

HistCite software is designed to aid researchers find the results of literature searches on the *Web of Science*. HistCite allows the viewer to analyze and organize the results of a search so as to obtain various aspects of the topic's structure, history, and relationships. It is easy, fast, and provides perspectives and information not otherwise available.

Dr Eugene Garfield, founder of the Institute for Scientific Information and the inventor of the Science Citation Index, © designed and developed HistCite software as an implementation of *algorithmic historiography*. Its main application is to enable individuals to perform bibliometric analysis and visualization tasks. Bibliometric analysis uses bibliographic information (titles, authors, dates, author addresses, references, etc.) within published items to measure and study various aspects of a specific field of scholarly endeavor.

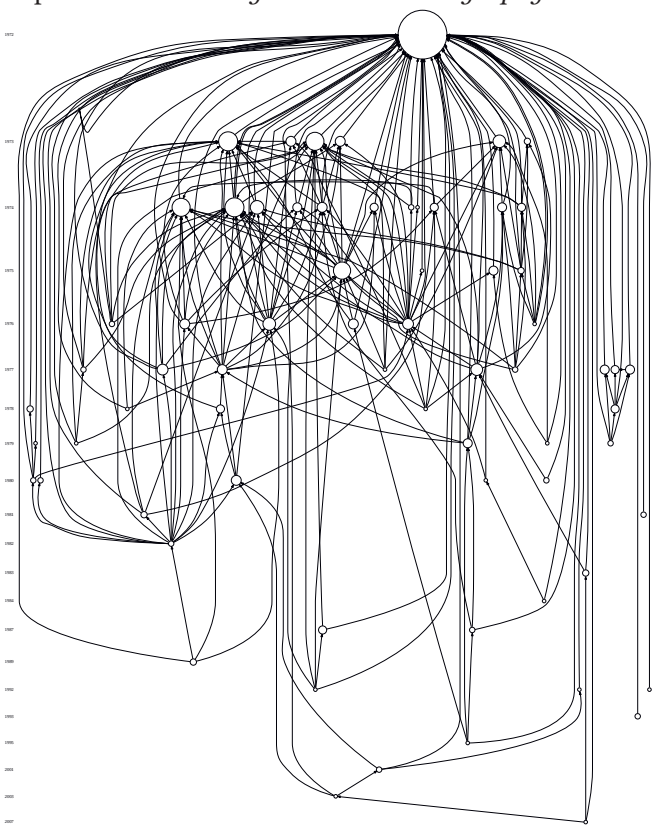


Figure 1. **HistCite historiography map obtained for the paper published in Circulation Research 1972. This historiography image that we converted to PDF format was done to obtain better printing quality.**

Figure 1 shows an example of the HistCite historiograph applied to papers that quote the publication entitled "Angiotensin I converting enzyme of the lung" that was published in *Circulation Research* (1972; Volume 31, pp. 51-61). Tables 1, 2, and 3 illustrate some other possibilities of HisCite. Dr. Garfield suggested that we use several of the most cited references from this publication "in order to give more historical depth and show the key papers prior to the Circ Res 1972 publication."

Frequent questions asked by bibliometricians and others that can be addressed by HistCite analysis include the following: How much literature has been published in this field of study? When, and in what countries, has it been published? What countries are the major contributors to this field? What are the languages most frequently used by authors who published the major papers? Who are the most prolific authors? What institutions do these authors represent? Which articles are the most important? The answers to such questions are important to researchers, librarians, and administrators of medical sciences.

HistCite software can be downloaded free of charge at Thomson Reuter's web site (registration required). To take full advantage of the software's features you will need access to the *Web of Science*s (WoS). To learn more about HistCite visit their Web Site at http://www.histcite.com.

Table 1. Partial list of papers citing Circ Res 1972 paper.

Records: 152, Authors: 347, Journals: 89, Cited References: 5092, Words: 478

Yearly output | Document Type | Language | Institution | Institution with Subdivision | Country

#	Date / Author / Journal	LCS	GCS	LCR	CR
1956					
1	1 SKEGGS LT, KAHN JR, SHUMWAY NP **THE PREPARATION AND FUNCTION OF THE HYPERTENSIN-CONVERTING ENZYME** JOURNAL OF EXPERIMENTAL MEDICINE. 1956; 103 (3): 295-299	39	665	0	10
1967					
2	2 ERDOS EG, YANG HYT **An enzyme in microsomal fraction of kidney that inactivates bradykinin** LIFE SCIENCES. 1967; 6 (15): 569-574	27	123	0	0
3	3 NG KKF, VANE JR **CONVERSION OF ANGIOTENSIN I TO ANGIOTENSIN 2** NATURE. 1967; 216 (5117): 762-&	29	438	1	23
1968					
4	4 BAKHLE YS **CONVERSION OF ANGIOTENSIN 1 TO ANGIOTENSIN 2 BY CELL-FREE EXTRACTS OF DOG LUNG** NATURE. 1968; 220 (5170): 919-&	33	191	1	12
1970					
5	5 YANG HYT, ERDOS EG, LEVIN Y **A DIPEPTIDYL CARBOXYPEPTIDASE THAT CONVERTS ANGIOTENSIN I AND INACTIVATES BRADYKININ** BIOCHIMICA ET BIOPHYSICA ACTA. 1970; 214 (2): 374-&	29	478	2	8
1971					
6	6 CUSHMAN DW, CHEUNG HS **SPECTROPHOTOMETRIC ASSAY AND PROPERTIES OF ANGIOTENSIN-CONVERTING ENZYME OF RABBIT LUNG** BIOCHEMICAL PHARMACOLOGY. 1971; 20 (7): 1637-&	55	1589	4	50

GCS - Global Citation Score, LCR - Local Cited References, LCS - Local Citation Score, CR - Cited References, Recs - Number of Records, T* - Total [score] Any Total score represents a sum of respected scores for all records from a given author, source, other category, or all records.

Table 2. Nine most cited references quoted in the paper that was published in the Circ Res 1972. That information gives more historical depth and shows the key papers prior to publishing the Circ Res 1972 paper.

	Author / Year / Journal	Recs	
1	IGIC R, 1972, CIRC RES, V31, P51	WoS	148
2	CUSHMAN DW, 1971, BIOCHEM PHARMACOL, V20, P1637	WoS	53
3	YANG HYT, 1971, J PHARMACOL EXP THER, V177, P291	WoS	49
4	SKEGGS LT, 1956, J EXP MED, V103, P295	WoS	34
5	BAKHLE YS, 1968, NATURE, V220, P919	WoS	29
6	YANG HYT, 1970, BIOCHIM BIOPHYS ACTA, V214, P374	WoS	28
7	DORER FE, 1972, CIRC RES, V31, P356	WoS	27
8	NG KKF, 1967, NATURE, V216, P762	WoS	25
9	ONDETTI MA, 1971, BIOCHEMISTRY-US, V10, P4033	WoS	25

Table 3. List of papers from various countries citing Circ Res 1972 paper

#	Country	Recs	TLCS	TGCS
1	USA	66	239	6640
2	Unknown	16	472	4783
3	JAPAN	11	13	299
4	FRG	10	21	312
5	UK	7	19	453
6	Germany	6	1	44
7	Italy	4	0	73
8	SWITZERLAND	4	5	140
9	TURKEY	4	0	6
10	USSR	4	0	45
11	YUGOSLAVIA	4	10	72
12	CANADA	3	0	30
13	DENMARK	3	2	39
14	AUSTRIA	2	0	36
15	BRAZIL	2	5	116
16	France	2	0	23
17	South Africa	2	1	26
18	AUSTRALIA	1	0	19
19	Bosnia & Herceg	1	0	3
20	GDR	1	0	7
21	HUNGARY	1	0	14
22	ISRAEL	1	0	3
23	Peoples R China	1	0	35
24	Russia	1	0	3
25	SWEDEN	1	0	5
26	Taiwan	1	0	35

Continuing Education Questions and Answers

Questions and Answers

Nada Đokanović, Nataša Stojaković, Nataša Tomić

Medical School
University of Banja Luka
Save Mrkalja 14
78000 Banja Luka
Republic of Srpska
Bosnia and Herzegovina

Ova rubrika (Q & A) sadrži neznatno izmenjene segmente iz navedene literature. Cilj nam je da tekst posluži čitaocu kao vežba za unapređenje stručnog engleskog jezika.

[This section presents short segments of texts from the Literature or original texts. The main purpose is to provide questions and answers that readers can use to improve their English.]

Scripta Medica

(Scr Med 2011;42:46-52)

Questions

1. What safety profiles play a decisive role in the race to identify novel anticoagulants designed to prevent stroke in patients with atrial fibrillation?

2. Who should be vaccinated in order to curb outbreaks of pertussis?

3. Current dependence on the laboratory, noninvasive testing, and interventional techniques for diagnosis diminishes the time and effort devoted to the medical history and physical examination. What is the future of bedside skills?

4. The average that represents the value of a total when shared equally is the

a. Mean
b. Median
c. Mode

5. The lower quartile of a distribution is such that

a. 1/4 of the values are greater than it
b. 1/4 of the values are less than it
c. 3/4 of the values are less than it

6. Half the values in a set of the data are less than the:

a. Mean
b. Median
c. Lower quartile

7. Which summary statistics are preferred when the distribution is roughly symmetrical?

a. Median and inter-quartile range
b. Mode and range
c. Mean and standard deviation

8. Two events A and B occur in such a manner that if B occurs, the probability of A is unchanged. The two events are said to be

a. Mutually exclusive
b. Exhaustive
c. Statistically independent

9. Twelve patients are treated with a drug to test its effectiveness. The variable of interest is the number of people who recover after taking the drug. The appropriate distribution to use this case is the

a. Binomial
b. Normal
c. Poisson

10. The distribution of the number of random events per unit time is

a. Poisson
b. Normal
c. Binomial

11. The distribution of the heights of adult male humans is likely to be

a. Binomial
b. Poisson
c. Normal

12. A random sample is one in which

a. Some members of the population are more likely to be picked than others
b. Each number of the population has an equal chance of being picked
c. Members of the population are picked because they are thought to be representative

13. A random sample is preferred by statisticians because it

a. Represents the entire population
b. Ensures against bias
c. Is chosen in a special statistical way

14. A 90% confidence interval for the mean of a population is such that

a. 10% of the values in the population lie outside it
b. There is a 90% chance that it contains all the values in the population
c. There is a 90% chance that it contains the mean of the population

15. If the sample size increases, the 95% confidence interval for the population mean will

a. Increase
b. Decrease
c. Remain the same

16. If we decide not to reject a null hypothesis (Ho) this

a. Proves that Ho is true
b. Proves that H1 is false
c. Implies that Ho is likely to be true

17. The *t* test for samples from a normal population must be used when

a. The sample size is small
b. The standard deviation is unknown
c. The sample size is small and the standard deviation is unknown

18. If the calculated value of χ^2 is less than or equal to the tabulated value of χ^2

a. H0 is rejected
b. H0 is not rejected
c. H1 is accepted

19. Linear regression is used to

a. Prove that there is a causal relationship between two variables
b. Predict one variable from the other
c. Show that as one variable increases so does the other

20. To investigate the relationship between certain solvents and cancer, all employees at a factory were questioned about their exposure to an industrial solvent, and the amount and length of exposure were recorded. The subjects were monitored regularly, and after 10 years, a copy of the death certificate for all those who had died was obtained. This is an example of a

a. Cohort study
b. Cross sectional study
c. Randomized controlled trial
d. Matched case control study
e. Quasi experimental design

21. A survey was conducted of all nurses employed at a particular hospital. Among the questions asked, was one about the grade of the nurse and whether she was satisfied with her career prospects. This is a

a. Cohort study
b. Cross sectional study
c. Randomized controlled trial
d. Matched case control study
e. Quasi-experimental design

22. To evaluate a new therapy, patients with lower back pain were randomly allocated to either the new treatment or to conventional occupational therapy. After three months they were questioned about their back pain and observed by independent monitors while lifting a weight. This is an example of a

a. Cohort study
b. Cross sectional study
c. Randomized controlled trial
d. Matched case control study
e. Quasi-experimental design

24. In a trial of the treatments for heart failure, 33% of the patients randomized to a group treated with ACE inhibitors died, whereas 38% of those randomized to groups treated with hydralazine and nitrates died. The point estimate of the difference between the groups is 5%. The 95% confidence interval around this difference is -1.2% to 12%. It is usually expressed in publications as: “The ACE inhibitor group had a 5% (95% CL -1.2 + 12) higher survival.” We may conclude that

a. An ACE inhibitor is the best choice for patients with heart failure (but that inference is weak)
b. There is no significant difference between the two treatments.
c. An ACE inhibitor is the appropriate choice for patients with heart failure (the strength of that inference is strong)

25. A meta-analysis is which of the following?

a. It provides an overview of primary studies that contains a statement of objectives, materials and methods, and has been conducted according to a particular and reproducible method.
b. It is defined as a statistical synthesis of the numerical results of several trials that all addressed the same question.
c. It does not synthesize the statistical results of other trials.
d. It is an overview of studies (review article) done on the same clinical subject.

26. The 2 x 2 table showing results of a validation study of urine glucose testing for diabetes compared to the gold-standard, the glucose tolerance test. Here a/a + c = 6/27 = 22.2% indicates which of the following?

a. Sensitivity, or how well this test identifies people who have the condition.
b. Specificity, or how well this test at correctly excludes people without the condition.
c. Positive predictive value. If a person tests positive, it indicates the probability that (s)he has the condition.
d. Negative predictive value. If a person tests negative, it indicates the probabilty that (s)he does not have the condition?

27. d/b + d = 966/973 = 99.3% indicates which of the following? (definitions given in question 26 above)

a. Sensitivity
b. Specificity,
c. Positive predictive value.
d. Negative predictive value.

28. a/a + b = 6/13 = 46.2% indicates which of the following?

a. Sensitivity
b. Specificity
c. Positive predictive value
d. Negative predictive value

29. d/c + d = 966/987 = 97.9% is which of the following?

a. Sensitivity
b. Specificity
c. Positive predictive value
d. Negative predictive value

30. An anesthesiologist measures the pain of a procedure using a 100 mm visual analog scale on his patients. He prepared dot plot of original and logged (loge) data from pain scores. The logged data show that the outlier does not appear as extreme as in the original. Indicate the incorrect answer

a. For the logged data the mean and median indicate a more symmetrical distribution
b. It is better to analyze logged transformed data by statistical tests than the original data
c. The antilog of the mean of the logged data is known as the geometric mean, and is often a better summary statistic than the mean for data from positively skewed distributions
d. The logged data is impossible to analyze in statistical tests.

31. Indicate the parametric test

a. Wilcoxon signed ranks test
b. Friedman two-way ANOVA
c. Mann-Whitney U test
d. Student's t-test

32. Indicate the non-parametric test

a. Analysis of variance (ANOVA)
b. Kruskal-Wallis ANOVA
c. Student's t-test
d. Repeated measures ANOVA

33. What are the properties of the best hand-carried ultrasound device in pediatric cardiology?

34. What are effects of topical or oral treatments in people with acne vulgaris?

35. Who introduced an expression *cognitive psychotherapy*?

36. What are the parts of a book?

37. What is the difference between print and electronic formats for journals?

38. Sudden onset of pain (beginning within a few seconds and immediately reaching maximal intensity) occurs with which of the following?

a. Appendicitis
b. Strangulated hernia
c. Cholecystitis
d. Spontaneous pneumothorax
e. Ruptured ectopic pregnancy

39. Which of the following factors probably contribute to the reduced diffusing capacity for CO in a patient with emphysema?

a. Loss of pulmonary capillaries
b. Reduced elastic recoil
c. Uneven distribution of ventilation, blood flow and diffusion properties

d. Increased FRC (functional residual capacity)

40. An inhaled foreign body most frequently enters

a. Left lung
b. Right lung
c. No difference

41. Which is true of bronchial carcinoma?

a. The disease has a higher prevalence in urban as opposed to rural communities.
b. The disease is more common in males than females.
c. The specific carcinogenic agent in cigarette smoke is known.
d. Pulmonary function tests are important in the early detection of the disease.
e. A carcinoma is always visible on a good chest radiograph.

42. Acidosis in respiratory failure is likely to be increased by

a. Depression of ventilation
b. Exacerbation of a chest infection
c. Peripheral circulatory failure
d. Renal retention of bicarbonate
e. Administration of morphine

43. A previously well young man was admitted to the emergency room with barbiturate poisoning, which caused severe hypoventilation. When he was given 50% O2 to breathe there was no change in his arterial PCO2. Approximately how much would his arterial P02 (in mm Hg) likely rise?

a. 25
b. 50
c. 75
d. 100
e. 200

44. Which of the following uses apply to a tracheostomy tube?

a. Facilitates the removal of secretions by suction
b. Provides a port for mechanical ventilation
c. Can be used to bypass a region of upper airway obstruction
d. Increases the anatomical dead space

Answers

1. Atrial fibrillation is the most common cardiac rhythm disorder. It affects more than 1% of the general population, and its prevalence rises up to 10% in people older than 80 years of age. This disorder is a major risk factor for ischemic stroke, irrespective of temporal pattern of AF, whether it is paroxysmal, persistent, or permanent. AF-related stroke confers significantly increased mortality and morbidity compared with non-AF causes of stroke.

Currently, aspirin and vitamin K antagonists (VKA) are the only approved antithrombotic therapies for stroke prevention in patients with AF. VKA therapy is recommended in patients with congestive heart failure, hypertension, age >75 years, diabetes, and a history of previous stroke/transient ischemic attack. However, the use of VKA necessitates regular anticoagulation monitoring. In addition, interactions of warfarin with food and other drugs also hamper its use. Patients remain within the therapeutic range for less than two-thirds of the time, and use of oral anticoagulant therapy is associated with a significant risk of major bleeding (approximately 2%/year). Antiplatelet therapy confers a similar or even greater risk of major bleeding when aspirin or aspirin-clopidogrel combination therapy is used.

A narrow therapeutic range and the need of regular monitoring of its anticoagulatory effect undermine the effectiveness and safety of VKA, requiring use of alternative anticoagulant drugs. Recently developed anticoagulants for patients at risk for stroke include direct thrombin antagonists such as dabigatron, factor Xa inhibitors such as rivaroxaban, apixaban, betrixaban and edoxaban, and novel vitamin K antagonists.

At this time, the only data available from a phase III clinical trial are for dabigatran only. The results show that a direct thrombin antagonist is similar to VKA in efficacy for the prevention of stroke and systemic embolism in patients with AF. Safety profiles play a decisive role in the race to identify the most successful anticoagulant, even when profiles of currently developed compounds indicate efficacy superior to that of VKA. Future clinical analyses will show whether direct inhibitors of factor Xa or thrombin have additional beneficial cardiovascular effects as suggested by pre-clinical data. An understanding of individual pharmacokinetic profiles, potential drug-drug, and drug-disease interactions will then allow us to translate the experimental results into improved effectiveness in real-world practice.

2. To battle outbreaks of pertussis, all caregivers and household contacts of infants should be vaccinated with tetanus toxoid, reduced diptheria toxoid and acellular pertussis (Tadp). According to new recommendations from the advisory committee at the US Centers for Disease Control and Prevention (CDC), vacinations should be given even if the person recently received tetanus and diptheria toxoid (Td) or cannot remember when they were immunized with either vaccine. It also recommended that individuals older than 65 years who care for infants and young children (ages of 7 - 10 years) should be vaccinated if their vaccination history is unclear.

Infants get their first in a five-dose series of combined vaccines called DTaP (diphteria, tetanus and cellular pertus-

sis) at 2 months and the last dose between 4 and 6 years. Children who were vaccinated early in life become susceptible again by age 11. Adolescents and young adults are also likely to spread this contagious bacterial infection, but this age group presents a less severe illness with only a persistant cough for few weeks. Consequently, these older patients may not be correctly diagnosed as having pertussis; in young infants the infection causes a distinct "whooping" sound with coughing.

Currently many parts of the USA experience epidemics of pertussis. California, had the worst pertussis outbreak since 1950s in 2010. (More than six thousand cases were reported from January to October with 10 infant deaths.)

3. The clinician needs both bedside skills and appropriately selected laboratory testing. Personal touch and high-tech medicine are not incompatible. When the physician uses them together, he or she is less likely to be misled.

A deficiency of clinical skills and critical thinking will become a serious problem if clinicians cannot pass along bedside skills to the upcoming generations of students. Observing basic clinical principles will help lead to the correct diagnosis and treatment.

There are many examples in the medical literature. Consider the following paragraph from "THINGS ARE NOT ALWAYS AS THEY SEEM" by Dr. Ira Martin Grais (Department of Medicine, Cardiology Division, Northwestern Feinberg School of Medicine, Chicago).

A middle-aged hypertensive man with a previous right nephrectomy for cancer was referred for a cardiac catheterization because of deep precordial T-wave inversions thought to be ischemic. He had no history of angina or dyspnea and was being treated for his hypertension. During the complete physical examination, a systolic bruit extending into diastole was heard over the left kidney, suggesting that the renal artery stenosis was the cause of the hypertension. Nonivasive imaging studies revealed an extrinsic mass compressing the left renal artery. At operation, the mass proved to be a solitary metastasis from his renal cancer. Postoperative blood pressures were normal, his T waves consistent with left ventricular strain improved, and the cardiac catheterization was deemed unnecessary.

Let us conclude with the words of Dr. Cheng:
Present-day physicians, especially gastroenterologists and cardiologists, rely too much on gadgets. The gastroenterologists like to pass scopes either from above or from below to make a diagnosis of peptic ulcer or ulcerative colitis, respectively, instead of taking a good history. Among cardiologists, I always like to use the diagnosis of mitral valve prolapse to illustrate gadgetophilia. Whenever this diagnosis is brought up on medical rounds, the 1st question the house staff asks is, "What did the echocardiogram show?"—instead of "What are the auscultatory findings?" The diagnosis of mitral valve prolapse, or Barlow's syndrome, was first made by John Brereton Barlow by clinical auscultation, not by echocardiography.

The use of a stethoscope is an art of medicine that is being lost amid growing reliance on gadgetry such as echocardiography, computed tomography, magnetic resonance imaging, and cardiac catheterization. A stethoscope weighs less than a pound, does not need an electric outlet or a video recorder, is not radioactive, has no adverse side effects, and fits easily into a coat pocket. Although the stethoscope is still being used by every physician, it is more an ornament than a diagnostic tool. Just witness all the popular television shows in which the only way to identify the doctors is from the stethoscopes wrapped around their necks, because doctors in the hospital usually do not wear uniforms nowadays.

Bedside rounds have been largely replaced by rounds held in conference rooms or auditoriums...Let us bring rounds back to the bedside, where history and physical examination, instead of reliance on laboratory tests, should play a major role in the management of our patients. As Fred said, "We need teachers who don't order expensive, state-of-the-art studies when cheaper, conventional tests supply the same information; Osler's maxim still pertains: "the four points of a medical student's compass are: Inspection, Palpation, Percussion, and Auscultation."

4. a 5. b 6. b 7. c 8. c 9. a 10. a 11. c 12. b 13. b 14. c 15. b 16. c 17. c

18. b 19. b 20. a 21. b 22. c 23. c 24. a 25. b 26. a 27. b 28. c 29. d 30. d

31. d 32. b

33. In pediatric cardiology modern techniques of ultrasound transmission and signal processing must provide high spatial and temporal resolution, because the anatomic structures are small, and heart rates are high. High-end electrocardiographic systems have the disadvantage of being bulky and heavy, making them difficult to handle in the setting of neonatal and pediatric intensive care units (ICU). Thus, hand-carried ultrasound (HCU) devices should reduce this disadvantage and combine good images with device flexibility. Several devices are commercially available. Dr. Dalla Pozza and colleagues (Munich, Germany) tested three such devices in the setting of a tertiary health care center, examining 110 children with cardiac disease in an outpatient clinic and an ICU. The weights of the devices (systems) are: Simens Acuson P10-0.725 kg, Simens Acuson P50- 5.4 kg, and Philips CX 50- 6.1 kg. The authors concluded that The Simens Acuson P10 system should be used with caution in small children with complex cardiac

disease. In the emergency care setting, however, it is very useful for rapid assessment of basic cardiac anatomy, cardiac function, and effusions. Two sophisticated HCU devices, the Simens Acuson P50 and the Philips CX 50, provided reliable images and measurements and can be fully recommended for use in children of any age with any cardiac defects. All three HCU devices are not fully mobile, as limited battery capacity necessitates frequent recharges.

34. Acne vulgaris is a common inflammatory pilosebaceous disease characterized by comedones, papules, pustules, inflamed nodules, superficial pus filled cysts, and (in extreme causes) canalizing and deeply inflamed, sometimes purulent sacs. Lesions are most common on the face, but the neck, chest, upper back, although shoulders may also be affected. The exact cause of acne is unknown. Four factors can contribute to acne development: increased sebum secretion rate, abnormal follicular diffentiation, causing obstruction of the pilosebaceous duct, bacterial infection of the pilosebaceous duct, and inflammation. Androgen secretion is the major trigger for adolescent acne, but the anaerobic bacterium *Propionibacterium acnes* is clearly involved in the pathogenesis of acne. Acne was the presenting complaint in 3.1% of people aged 13-25 years attending primary care in a UK population. The overall incidence is similar in both men and women, and peaks at 17 years of age.

Beneficial topical treatments include: benzoyl peroxide (primarily in people with moderate acne), clindamycin (reduces the number of inflammatory lesions in mild to severe acne), erythromycin (mild to severe acne), tretinoin (mild to moderate acne; topical retinoids are not used in pregnancy or by women of childbearing age who could become pregnant).

Likely to be beneficial topical treatments: adapalene, azelaic acid, isotretinoin, tetracycline.

Unknown effectiveness of topical treatments: meclocycline.

Likely to be beneficial oral treatments: erythromycin. Trade of between benefits and harms of oral treatments: doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline.

In the absence of treatment, acne persists in most sufferers for an average of 8-12 years.

35. An expression 'cognitive psychotherapy' was introduced by Richard B. Brandt, an American philosopher, in a *Theory of the Good and the Right* (1979) to refer to a process of assessing and adjusting one's desires, aversions, or pleasures. This process is central to Brand's analysis of rationality, and ultimately, to his view on the justification of morality.

Brandt characterizes the key definitions as follows: (1) available information; (2) information is relevant provided, if the agent were to reflect repeatedly on it, "it would make a difference," i.e., would affect the attitude in question, and the effect would be a function of its content, not an accidental byproduct; (3) relevant information is represented in an ideally vivid way when the agent focuses on it with maximal clarity and detail and with no hesitation or doubt in its truth; and (4) repeatedly and at appropriate times refer, retrospectively, to the frequency and occasions that would result in the information's having the maximal attitudinal impact. Suppose Mary's desire to smoke were extinguished by her bringing to the focus of her attention, whenever she was about to inhale smoke, some justified beliefs, say that smoking is hazardous to one's health and may cause lung cancer; Mary's desire would have been removed by cognitive psychotherapy.

[In psychology, thought or thought processes are called *cognition* or *cognitive processes*, the mental processing of information including memorizing, reasoning, problem solving, conceptualizing, and imagining.

According to the Webster's dictionary *Cognition* means: 1. the act or process of knowing, perception, 2. the product of such a process; something thus known, perceived, 3. knowledge. *Cognitive* means: 1. of or pertaining to cognition, 2. of or pertaining to the mental processes of trusted with emotional and volitional processes.

Cognitive therapy (also called *cognitive behavior therapy)*: a form of therapy for depression in which the goal is to diminish symptoms by correcting distorted thinking based on negative self-perceptions and expectations.]

36. Books are traditionally organized into three major divisions: the front matter (also called preliminary matter, or prelims), the text, and the back matter (or end matter). The front matter gives information about a book title, publisher and copyright; it acknowledges debts to the work of others; it provides a way to navigate the structure of the book; and it introduces the book and sets its tone. The text proper comprises the narrative—including arguments, data, illustrations, and so forth—often divided into chapters and other meaningful sections. The back matter presents sources or sources notes, appendixes, and other types of documentation supporting the text but outside its central focus or narrative.

In the traditional arrangement, lowercase roman numerals are used for pages in the front matter and Arabic numerals for the rest, including the back matter. Every page is counted in the page sequence, even those on which no number actually appears, such as the title and half-title pages, copyright page, and blank pages. Modern books are paginated consecutively, and all pages except endpapers (one or two sheets of paper appearing at the beginning and

end of a hardcover book that are glued against the inside of the cover) are counted in the pagination whether or not the numbers appear.

[Publishers refer to the trimmed sheets of paper that you turn in a printed-and-bound book as leaves, and a page is one side of a leaf. The front of the leaf, the side that lies to the right in an open book, is called the recto. The back of the leaf, the side that lies to the left when the leaf is turned, is the verso. Rectos are always odd-numbered, versos always even-numbered. In an electronic book, the distinction between rectos and versos can be represented or simulated but need not be.]

37. The majority of scholarly journals are produced either in print and electronic versions or as electronic-only journals, though many print-only journals persist, mainly in nonscientific fields. Electronically published journals usually contain all the material included in any printed counterpart except, in some cases, advertising. Electronic journals typically present the material in one of two ways (and often both): (1) as searchable page images suitable for printing by the end user and corresponding to the pages of the journal's print issues (i.e., as a PDF); or (2) as full-text HTML versions suitable for viewing in a web browser and containing features and supplementary materials not available in the print edition.

Although a printed article should include all elements that are essential to understanding, interpreting, and documenting the text, many journals publish special materials electronically that are not available in the print version. These features may include very large tables, supplemental reading lists, audiovisual components, large data sets that can be exported to third-party software for analysis, or color versions of figures published in black and white in the printed journal; some of this material may constitute the basis of an outline-only appendix. Appendices and other features must be listed in the print version (either in the table of contents or on the first page of the applicable article), and the differences between the print and electronic versions must be made apparent in the latter.

38. d, e 39. a, c 40. b 41. a, b 42. a, b, c, e 43. e 44. a, b, c

Literature

1. Anonymous. The Chicago manual of style. Chicago and London: University of Chicago Press, 2010.
2. Anonymous. Webster's unabridged dictionary, second edition. New York, Random House, 2001.
3. Audi R (ed). The Cambridge dictionary of philosophy, second edition. Cambridge, Cambridge University Press, 2006.
4. BMJ Publishing Group. Clinical evidence concise. London, BMJ, 2006.
5. Cheng TO. Hyposkillia: deficiency of clinical skills (Letter to the Editor). Tex Heart Inst J. 2005;32:623-4.
6. Dalla Poza R et al. Hand-carried ultrasound devices in pediatric cardiology: Clinical experience with three different devices in 110 patients. J Am Soc Echocard 2010;23:1231-7.
7. Fred HL. Hyposkillia: deficiency of clinical skills. Tex Heart Inst J 2005;32:255-7.
8. Gelin LE, Nyhus LM, Condon RE. Abdominal pain. A guide to rapid diagnosis. Philadelphia, Lippincott, 1969.
9. Grais IM. Bedside skills. A 50-year personal retrospective. Tex Heart Inst J 2010;37:629-32.
10. Greenhlagh T. How to read a paper. The basics of evidence-based medicine, third edition. London, BMJ, 2006.
11. Kuehn BM. Panel backs wider pertussis vaccination to curb outbreaks, prevent deaths. JAMA 2010;304:2684-6.
12. Rees DG. Essential statistics, third edition. London, Chapman & Hall, 1995.
13. Schimer S H et al. Novel anticoagulants for stroke prevention in atrial fibrillation. Current clinical evidence and future developments. J Amer Coll Cardiol 2010;56:2067-76.
14. Swinscow TDV, Campbell MJ. Statistics at square one, ninth edition. London, BMJ, 1996.
15. West JB. Pulmonary pathophysiology—the essentials. Third edition. Baltimore, Williams and Wilkins, 1987.

Apstrakti radova publikovanih u stranim časopisoma

Eur J Clin Pharmacol. 2010; 66:177-86. .

Outpatient utilization of drugs acting on nervous system: a study from the Republic of Srpska, Bosnia & Herzegovina.

Marković-Peković V, Stoisavljević-Satara S, Skrbić R.

Health Insurance Fund, Republic of Srpska, Banja Luka, Bosnia and Herzegovina.

ABSTRACT

PURPOSE. The aim of this study was to analyse the utilization patterns of drugs acting on the nervous system in the Republic of Srpska, Bosnia & Herzegovina between 2002 and 2008.

METHODS. This was a retrospective study aimed at analysing outpatient utilization of drugs reimbursed by the Health Insurance Fund, with a focus on the utilization of drugs acting on the nervous system. Anatomical therapeutic chemical/defined daily dose methodology was used to monitor drug utilization, and the drug utilization 90% (DU90%) method was used to assess drug prescribing.

RESULTS. The most highly used drug subgroups were psycholeptics and antiepileptics followed by the psychoanaleptics. Anxyolitics comprised the most prescribed pharmacological subgroup over the whole study period, but a decrease was observed in 2007 and 2008. Following updating of the list with selective serotonin re-uptake inhibitor drugs, particularly sertraline, antidepressant use increased fivefold in 2008 compared to 2006. Tramadol was the predominant opioid analgesics in terms of utilization, while the use of oral morphine was low. Diazepam was the most highly prescribed drug, followed by phenobarbital and carbamazepine. The list update with the new generation drugs was immediately reflected in the DU90% profile.

CONCLUSIONS. The observed tendency toward increased total drug utilization observed in our study is comparable to worldwide trends. Implementation of new clinical guidelines for nervous diseases and updating of the list of reimbursable drugs with the addition of new ones contributed to the observed improvement in prescribing patterns in primary healthcare during the study period. The DU90% is shown to be a simple rough method for assessing prescribing quality. More stratified analyses should be performed on a routine basis to ensure a rational use of medicines and a cost-efficient use of limited healthcare resources.

Psychiatria Danubina, 2011; Vol. 23, No. 1, pp 64–68
Brief report

EATING ATTITUDES IN ADOLESCENT GIRLS

Marija Radmanović-Burgić[1], Živana Gavrić[2] & Sanela Burgić[3]
[1]Department of Psychiatry, Medical Faculty , University Banja Luka, Bosnia and Herzegovina
[2]Department of Social Medicine, Medical Faculty , University Banja Luka, Bosnia and Herzegovina
[3]Medical Faculty, University Banja Luka, Bosnia and Herzegovina

received: 28.07.2010; revised: 11.12.2010; accepted: 29.1.2011

SUMMARY

Introduction: *Eating disorders are more common in women; especially adolescent girls are at risk. Our objective was to assess whether the adolescent girls were satisfied with their present physical appearance and weight and to analyze their views about their appearance.*

Subjects and methods: *The survey was conducted among female adolescents, aged 16–17, in all secondary schools in Banjaluka, using the Eating Attitudes Test - EAT-26. The response rate was 1956 (87.3%) out of 2240 (total number in the first and second grade female students).*

Results: *Almost half of the students surveyed with BMI <18.5 kg/m² were sometimes dissatisfied with their body image. More than half (54.8%) with BMI 18.5-25 kg/m² were sometimes dissatisfied with their appearance, while 1 of 10 respondents had that feeling often. Nearly 20% declared that they often wanted to be slimmer. With statistically significant differences, the surveyed students with BMI <18 kg/m² stated that they were unaware of calorie value of foods in comparison to students with BMI of 18-25 kg/m² (χ^2=63.7, df=24, p=0.000). Nearly 33% of respondents were always, very often, and often familiar with food calorie values.*

Discussion: *Unrealistic idea of the body size can bring out various health risks. The health risks ranges from inadequate child attempts to inability to recognize and stop the weight gain.*

Conclusion: *The survey highlights a need for education of young people in order to accept a healthy lifestyle.*

Pneumologia. 2011 Jan-Mar;60(1):36-9.

Changes in spirometry over time in uraemic patients receiving long-term haemodialysis therapy.

Kovacević P, Stanetic M, Rajkovaca Z, Meyer FJ, Vukoja M.

Medical Intensive care unit, University Hospital Banja Luka, Republika Srpska, BiH.

ABSTRACT

Complications of respiratory system in patients suffering from chronic renal failure who are treated with regular haemodialysis are well known. However, the influence of the duration of haemodialysis on pulmonary function is less understood. The aim of this study was to determine spirometry changes in patients on chronic haemodialysis over a five-year period. We tested 21 patients, out of which 11 female and 10 male, mean age of 50 (+/- 11) years. The mean duration of haemodialysis was 52.2 (+/- 44.7) months at the time of the inclusion. We performed spirometry testings in all patients, one hour before start and one hour after completion of haemodialysis. All parameters of spirometry recorded one hour after completion of haemodialysis (FVC, FEV1, FEF75, 50, 25, % of predicted), improved significantly ($p < 0.01$). After five years, only FVC demonstrated significant decline and none of the recorded spirometry parameters improved significantly one hour post haemodialysis compared to pre-haemodialysis period. Analysis of post-dialysis parameters of spirometry at the study onset and following five years of haemodialysis showed that all parameters, except FEF50 ($p > 0.05$), significantly deteriorated ($p < 0.01$). Patients who are on long-term haemodialysis show a significant decline in FVC following five years of treatment. Although the spirometry changes in observed population treated with chronic haemodialysis have reversible character during the first years of renal replacement therapy, five years after these changes become irreversible.

Digestive and Liver Disease 43 (2011) 478–483

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Step-up approach to infected necrotising pancreatitis: A 20-year experience of percutaneous drainage in a single centre

Enver Zerem*, Goran Imamović, Alma Sušić, Bahrija Haračić

University Clinical Center, Tuzla, Bosnia and Herzegovina

Zerem E i sar. Minimalno invazivni tretman akutnog infetivnog nekrotizirajućeg pankreatitisa: 20 godina iskustva sa perkutanom drenažom u tretmanu teških oblika akutnog pankreatitisa

Akutni pankreatitis je bolest sa širokim dijapazonom kliničkih manifestacija i može se prezentirati od relativno blagog kliničkog oblika do veoma teškog hemoragijsko-nekrotičnog stanja sa visokim procentom smrtnog ishoda. Oko 10-20% pacijenata sa akutnim pankreatitisom razviju tešku formu bolesti, koju karakterišu opsežne intrapankreatične i peripankreatične nekroze. U tim slučajevima smrtnost je između 10-40%, a ako se razvije infekcija nekroza sa sepsom i multiorganskom insuficijencijom smrtnost prelazi 50%.

Adekvatan tretman inficiranih pankreasnih nekroza još uvijek je diskutabilan. Ranije se smatralo da je urgentna hirurška nekresektomija, u cilju uklanjanja devitaliziranog tkiva i kontrole sepse, metoda izbora kod ovih bolesnika. Ali, vremenom se uvidjelo da je, u početku bolesti, vrlo teško razganičiti nekrotično od normalnog tkiva i da su komplikcije (krvarenje i eskalacija multiorganske insuficijencije) u toku i neposredno nakon hirurške intervencije relativno česte a ponekad i smrtonosne.

Zadnjih godina, tretman akutnog nekrotizirajućeg pankreatitisa sve više je usmjeren ka minimalno invazivnim laparoskopskim i drenažnim procedurama. Minimalno invazivni tretman, bilo samo konzervativni suportivni ili uz primjenu laparoskopskih i drenažnih metoda, ima za cilj da klasičnu hirurgiju izbjegne ili je bar odloži do konsolidacije bolesti.

Autori ovog članka su u retrospektivnoj studiji evaluirali svoje dvadesetogodišnje iskustvo u tretmanu ove teške bolesti. Značaj studiji daje činjenica da se radi o izuzetno teškoj bolesti, sa čestim smrtnim ishodom, oko čijeg je tretmana uvijek bilo, a još i danas ima, značajnih kontraverzi.

Od 371 pacijenta, koji su liječeni u ovoj bolnici od akutnog pankreatitisa, u studiju je uključeno 86 pacijenata sa teškim oblikom akutnog pankreatitisa i posljedičnom akutnom inficiranom nekrozom potvrđenom mikrobiološki ili prisustvom gasa na CT-u. Pacijenti su liječeni u početku konzervativnim tretmanom sa suportivnim mjerama u smislu nadoknade tečnosti i elektrolita i u jedinicama intenzivne njege dok je to opšte zdravstveno stanje pacijenta zahtijevalo. U slučaju neuspjeha konzervativnog tretmana primjenjivana je perkutana drenaža uz ostali intenzivni tretman a samo u slučajevima neuspjeha i konzervativnog i drenažnog tretmana, pristupalo se hirurškoj nekresektomiji.

Rezultati studije pokazali su da se kombinacijom konzervativnog i drenažnog tretmana infektivnog nekrotizirajućeg pankreatitisa, uspjeh može postići a hirurška nekresektomija izbjeći u 84.9% bolesnika. Upoređujući svoje rezultate sa podatcima iz literature i dokumentujući da su uključeni pacijenti imali najteži oblik akutnog pankreatitisa, autori zaključuju da se smrtnost od 9,3% i konverzija u hirurški tretman od 12,8% mogu smatrati prihvatljivim. U zaključku autori, konstatuju da ovakav, minimalno invazivni menadžment, često može omogućiti uspješan oporavak bolesnika, oboljelih od najtežeg oblika akunog pankreatitisa i izbjegavanje vrlo teških i rizičnih hirurških intervencija.

Uređivački odbor časopisa „Digestive and Liver Disease“ (IF-2,972), ukazao je priznanje autorima članka stavljajući naslov članka, kao jedinog originalnog članka u junskom izdanju, na naslovnu stranicu. Istovremeno, profesor Mark Besselink, voditelj „Dutch Acute Pancreatitis Study Group” i jedan od najvećih svjetskih eksperata iz oblasti pankreatologije dao je svoj komentar ovog članaka na dvije stranice u istom broju časopisa, ukazujući da su rezultati njihovih nedavnih multicentričnih studija saglasni sa stavovima iznesenim u ovom članku.

Journal of BUON **16:** 170-173, 2011

ORIGINAL ARTICLE

Pulse carboxyhemoglobin-oximetry and cigarette smoking

L. Sokolova-Djokić[1], S. Milošević[2], R. Škrbić[3], R. Salabat[2], G. Voronov[2], R. Igić[2,3]

[1]Department of Public Health, Sombor, Serbia; [2]Department of Anesthesiology and Pain Management, John Stroger Hospital of Cook County, Chicago, USA; [3]Department of Pharmacology, Toxicology, and Clinical Pharmacology, Medical Faculty, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Pulsna karboksihemoglobinska oksimetrija i pušenje cigareta

Pomoću pulsnog oksimetra za određivanje ugljen monoksida (CO) merili smo nivo karboksihemoglobina (COHb) u pušača i nepušača. Cilj je bio da ustanovimo može li taj uredjaj ne samo definisati pušački status već i poslužiti da se poveća tacnost izjava koje pri anketiranju daju pušači.

U ovoj studiji su učestvovala 34 zdrava volontera. Dvadeset i dva su učesnika bili pušači koji su svakodnevno pušili, a 12 su bili nepušači koji su živeli sami ili zajedno s nepušačem i radili u ambijentu bez duvanskog dima. Nivo zavisnosti od nikotina je određivan pomoću Fagerstromovog upitniku. Nivo COOHb je meren pomoću pulsnog CO oksimetra (Masimo, Radical 7).

Nivo COHb u umerenih/teških pušača i lakih pušača bio je značajno povišen nakon što su popušili jednu cigaretu. To povišenje je trajalo duže od 6 sati u umerenih/teskih pušača, a kod lakih pušača COHb nivo se vraćao na početni nivo nakon jednog sata (Tabela 1).

Zaključili smo da pomoću CO-oksimetra možemo ustanoviti da li je umereni/teški pušač pušio do pre 6 sati, a laki do pre 20 minuta. Proizilazi da se ovaj metod može koristiti za validaciju pušenja u vreme ulaska pacijenta u hirušku jedinicu pa to može poslužiti za podsticanje apstinencije tokom preoperativnog i postoperativnog perioda. Taj jednostavan, neinvazivan i jeftin test mogao bi se primenjivati i pri anketiranju pušača jer bi se tako povećala tačnost izjava o pušačkom statusu ispitanika.

Table 1. Pulse oximetry measurements of carboxyhemoglobin levels in healthy cigarette smokers and non-smokers

Group	*n*	*Levels of carboxyhemoglobin (%)*		*p-value**
		Range	*Mean (SD)*	
Non smokers	12	0-2	0.7 (0.8)	–
Moderate/heavy smokers	11			
12 h abstinence		0-2	1.4 (0.8)	NS
Post smoking**				
20 min		3-13	6.1 (2.9)	< 0.001
60 min		2-8	4.8 (2.0)	< 0.001
3 h		2-4	3.2 (0.9)	< 0.001
6 h		2-4	2.9 (0.8)	< 0.001
Light smokers	11			
12 h abstinence		0-1	0.8 (0.6)	NS
Post smoking**				
20 min		1-4	2.1 (1.1)	< 0.005
60 min		0-2	1.2 (0.6)	NS
3 h		0-1	0.6 (0.7)	NS
6 h		0-1	0.7 (0.5)	NS

The smokers were classified into two groups according to the nicotine dependency score: "light smokers" (a score of 3 points or less) and "moderately/heavy smokers" (a score of 4 points or more). *smokers vs. non-smokers; **the time after one cigarette was smoked; NS: not significant; n: number of subjects.

New Books/Nove knjige

Amin MB et al. Diagnostic pathology: Genitourinary. Altona Manitoba, Amirsys, 2010. ISBN 978-1-931884-28-0

Bhugra D, Craig T, Bhui K. Mental health of refugees and asylum seekers. Oxford, Oxford University Press, 2010 (308 pages). ISBN 978-0-19-955722-6

Bilous R, Donnelly R. Handbook of diabetes, fourth edition. Chichester, Wiley, 2010 (238 pages). ISBN 978-4051-8409-0

Campbell MJ, Swinscow TDV. Statistics at square one, tenth edition. London, BMJ, 2009

Chisholm-Burns MA et al. Pharmacotherapy: Principles and practice, second edition. New York, McGraw Hill Medical, 2010 (1869 pages). ISBN 978-0-07-162180-9

Gould BE, Dyer RM. Pathophysiology for the health professions, fourth edition. St. Louis, 2011 (706 pages). ISBN 978-1-4377-0965-0

Himmelfarb J, Sayegh MH. Chronic kidney disease, dialysis, and transplantation. Companion to Brenner and Rector's The Kidney. Philadelphia, Saunders, 2010 (737 pages). ISBN 978-1-4377-0987-2

Kažić T. Neurofarmakoterapija psihofarmakoterapija, drugo izdanje. Beograd, Integra, 2010 (253 strane). ISBN 978-86-87907-03-4. www.eknjizara.rs/medicina

Kažić T. Farmakologija, šesto izdanje. Beograd, Integra, 2011 (465 strana). ISBN 978-86-87907-07-2. www.eknjizara.rs/medicina

Kažić T. Klinička farmakologija - farmakoterapija. Beograd, Integra, 2011 ISBN 978-86-87907-09-6

Lang RM et al. Dynamic ehocardiography. St. Louis, Sanders, 2011 (475 pages). ISBN 978-1-4377-8

Porter RS (ed.). The Merck manual online. Also available as a printed book. http://www.merckmanuals.com/professional/index.html. (Use: The Merck manual of diagnosis and therapy.)

Ross MH, Pawlina W. Histology. A text and atlas with correlated cell and molecular biology, sixth edition. Philadelphia, Walters, 2011 (974 pages). ISBN 978-0-7817-7200-6

Ruger JP. Health and social justice. Oxford, Oxford University Press, 2010 (276 pages). ISBN 978-0-19-955997-8

Schemitsch EH, McKee MD. Operative techniques: Orthopedic trauma surgery. Philadelphia, Saunders, 2010 (927 pages). ISBN 978-1-4160-4935-7

Seidel HM et al. Mosby's physical examination handbook. St. Louis, Mosby, 2011. ISBN 978-0-323-06540-5

Spasovski D. Funkcionalna anatomija čoveka. Novi Beograd, Excelsior, 2009 (171 strana). ISBN 987-86-82-659-33-4

Šibalić S. Antimikrobna terapija starijih osoba. Tuzla, PrintCom. 2010 (500 strana). ISBN 978-99-58-13-045-8

Vulić D., Babić N. Hronične nezarazne bolesti. Prevencija i kontrola. Banja Luka, Medicinski fakultet, 2011 (360 strana).

Waldman SA, Terzic A. Pharmacology and therapeutics. New York, Elsevier, 2009 (1054 pages). ISBN 978-1-4160-6098-7

Uputstvo autorima

Scripta Medica je internacionalni časopis koji objavljuje originalne članke (klinička, laboratorijska i epidemiološka istraživanja), ali i članke koji imaju za cilj da edukuju i obavijeste ljekare i stručnjake srodnih disciplina.

Na engleskom ili srpskom jeziku, časopis objavljuje radove o originalnim istraživanjima, pregledne članke, istorijske članke, uvodnike, rješavanje kliničkog problema, prikaze slučajeva i slike iz kliničke medicine (images in clinical medicine). Prednost imaju članci napisani na engleskom jeziku. Samo na srpskom jeziku se objavljuju specijalna saopštenja (edukativni članci i članci koji ukazuju na savremene trendove u medicini), prikazi knjiga, vijesti, izvještaji sa stručno-naučnih skupova i prevodi izvoda članaka domaćih autora koji su objavljeni u međunarodnim časopisima. Izuzetno, edukativni članci mogu biti pisani na engleskom jeziku. Uvodnici donose komentare objavljenih članaka u časopisu ili izražavaju stavove Uređivačkog odbora. Ove članke pišu urednici časopisa ili stručnjaci po narudžbi urednika.

Ovo uputstvo je sastavljeno prema vodiću "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (www.icmje.org).

Kako se šalje rukopis
Rukopis se šalje elektronski na sljedeću e-adresu:
editor@scriptamedica.com

Rukopis i propratno pismo treba slati u 'word' programu, a slike u JPG ili TIFF formatu. Od autora se traži da u popratnom pismu predlože dva ili više potencijalnih recenzenata, stručnjaka koji posjeduju značajno iskustvo s predmetom predloženog rukopisa, ali taj prijedlog nije obavezan. Svaki rukopis mora imati autora s kojim se vrši dopisivanje (Corresponding Author), a on piše i popratno pismo uredniku u kome navodi da je materijal originalan, da nije publikovan i da nije poslat u neki drugi časopis. Izuzetak su skraćeni prevodi radova na srpski jezik koji su objavljeni u poznatim međunarodnim časopisima. Autor s kojim se vrsi dopisivanje mora za originalnao istrazivanje, revijski clanak, specijalni clanak, prikaz slucaja i resavanje klinickog problema dati izjavu o potencijalnom konfliktu interesa za sebe i koautore rukopisa.

Recenziranje rukopisa
Rukopisi se prvo recenziraju od strane uređivačkog tima tako što ih pregledaju najmanje dva urednika. Potom se odabrani rukopisi šalju recenzentima. Kada se izvještaji recenzenata vrate uredništvu, urednik šalje pismo autoru s odgovarajućom odlukom i izvještajima recenzenata. Nastojimo da u roku od tri mjeseca od prijema rukopisa bude donijeta konačna odluka. Razlog za odbijanje rada može biti manjak originalnosti, veće greške načinjene tokom istraživačkog postupka, izostanak jasne poruke o značaju tog istraživanja ili procjena da članak nije interesantan za čitaoce časopisa.

Priprema rukopisa
Rukopisi se pišu s duplim proredom. Rukopis članka o vlastitom istraživanju izgleda ovako: Prve dvije strane su naslovna strana i apstrakt s ključnim riječima, slijede stranice na kojima se piše uvod, materijal i metode, rezultati i reference. Pored toga, rukopisu se odvojeno prilažu tabele, ilustracije i legende.

Rukopis preglednog članka, pored naslovne strane i apstrakta, sadrži poglavlja koja značajno variraju u zavisnosti od predmeta koji obrađuje članak. Prikaz slučaja sadrži sljedeće dijelove: naslov (kratak i deskriptivan), uvod, opis slučaja (ili više njih), diskusiju, zaključak i reference (ne više od 6). Uvod treba da je veoma kratak. Prikaz slučaja može imati najviše pet autora. Specijalni članci uključuju istorijske teme, edukaciju, demografiju, savremene teme iz zdravstva, rješenje kompleksnog kliničkog problema i sl. Dodatne instrukcije za specijalne članke mogu biti dobijene od urednika.

Naslovna strana rukopisa, pored naslova, sadrži imena i prezimena autora, nazive ustanova u kojima je obavljeno istraživanje, mjesto (državu) i adresu, telefone i *e-mail* autora zaduženog za korespodenciju.

Naslov članka o vlastitom istraživanju treba da bude informativan, kratak (da sadrži manje od 17 riječi) i jasan. U njemu se ne pišu skraćenice i nepotrebne („prazne") riječi. Naslov treba da je jasan kada stoji sam. Čitaoci treba da saznaju predmet saopštenja, a ne detalje sadržaja. Zato naslov samo ukazuje na ono o čemu je riječ, a ne kakvi su nalazi ili zaključci.

Za članke na srpskom ili engleskom jeziku piše se strukturisani apstrakt informativnog tipa (do 250 riječi). Strukturisan apstrakt sadrzi ove dellove: uvod, metode, rezultati i zaključak. Na posebnoj strani se piše naslov rada i tekst sa sljedećim podnaslovima: uvod i cilj rada, metode (uključujući izbor ispitanika, laboratorijskih životinja, tkiva ili ćelijskih kultura), rezultati i zaključak. Ispod aspstrakta, autori treba da navedu 3-8 riječi ili kratkih fraza. Treba koristiti termine koje koristi *Index Medicus* za "Medical Subject Headings". Za pregledni članak i specijalne članke koji se odnose na istorijske teme, apstrakt je nestrukturisan, indikativnog tipa, a piše se u jednom pasusu (do 150 riječi) na srpskom i engleskom. Za ostale tipove članaka apstrakt se ne piše. Rukopisi originalnih istraživanja treba da sadrže ova poglavlja: uvod, materijal i metode, rezultati, diskusija i reference.

Uvod

Glavni cilj uvoda je da se čitaocu saopšti zašto je vršeno to istraživanje - da se rasvijetli neka nejasnoća, razriješe konfliktna zapažanja ili da se na neki drugi način dopuni postojeće znanje. Zato se u uvodu uvijek postavlja istraživački problem tj. pitanje na koje se traži odgovor. Problem se ne mora postaviti baš u formi pitanja, već se svrha istraživanja može tako navesti da se iz nje jasno uočava pitanje. Na primjer: "Cilj ovog istraživanja je da se uporedi preživljavanje nakon godinu dana od početka liječenja metastaskog karcinoma prostate novom kombinacijom hemoterapijskih lijekova sa standardnom kombinacijom." Cilj istraživanja se, takođe, može navesti kao testiranje hipoteze.

U uvodnom dijelu članka treba citirati samo najvažnije reference kojima se opravdava to istraživanje. Najbolje je izabrati radove različitih istraživačkih grupa, pogotovo ako su iz različitih zemalja. Predlažemo autorima da pišu uvod ne više od tri pasusa.

Materijal i metode

Opis metoda treba da ima logički slijed koji kazuje kakav je dizajn studije, kako je izvedeno istraživanje (opisati ispitanike ili eksperimentalne životinje, randomizaciju, navesti podatke o korišćenim materijalima, dati tačne doze i način davanja lijekova, detaljno opisati neuobičajene aparate, navesti saglasnost lokalnog etičkog komiteta za ispitivanja na ljudima i životinjama), kako su dobijeni podaci, kako su oni prikazani i koji su testovi korišćeni za statističku analizu. Procedure i eksperimente treba tako opisati da ih drugi istraživači mogu ponoviti. Korišćene metode koje su ranije opisane treba skraćeno opisati, uz navođenje reference. Često primjenjivane kliničke i laboratorijske metode, kao i uobičajene statističke operacije se ne opisuju, a za složenije statističke metode treba navesti reference. Jedinice mjere za dužinu i težinu se izražavaju metričkim sistemom, a laboratorijski i klinički podaci se navode u jedinicama SI sistema, s tim da se uobičajene metričke jedinice mogu staviti u zagradu. Novije statističke metode treba opisati s dovoljno detalja da čitaoci mogu verifikovati saopštene rezultate. Detalje randomizacije treba navesti, dati broj opservacija, navesti statistički program, ako je takav korišćen, opisati metod određivanja veličine uzorka

Rezultati

Dobijeni rezultati se prikazuju tekstualno, tabelama i ilustracijama. U tekstu se ukazuje na najznačajnije rezultate i njega obično prati tabelarni prikaz podataka. U tabelama se ne smije duplirati informacija koja je data u tekstu ili ilustracijama. Kod sumiranja podataka u poglavlju Rezultati, navesti metode statističke analize. Pošto su standardna devijacija (SD) i standardna greška srednje vrijednosti (SE) pozitivni brojevi, prihvatili smo uputstvo Komiteta naučnih urednika (Council of Science Editors: *Scientific Style and Format*, 2006) da ± znak kod prikazivanja SD i SE bude eliminisan. Zato se ti podaci pišu u zagradi. Na primjer, vrijednosti za sistolni krvni pritisak kod 87 studenata piše se ovako: "Srednja vrijednost sistolnog krvnog pritiska bila je 129 mmHg (SD = 6, n = 87).

Ilustracije se koriste samo ako se dobijeni rezultati ne mogu jasno prikazati na drugi način. Fotografije treba da budu najboljeg kvaliteta. Fotografije u boji se objavljuju, a njihovo štampanje se ne naplaćuje. Mikrosopske slike se prilažu uz navođenje tehnike bojenja, a skala se mora nalaziti na samoj fotografiji. Slajdovi (u PowerPointu) nisu najpogodniji za kvalitetnu reprodukciju. Za korišćenje već objavljenih tabela i ilustracija, autor mora pribaviti pismenu saglasnost od nosioca zaštićenog prava (obično izdavač) i autora. Sve ilustracije nose naziv "Slika" i one se numerišu redoslijedom njihovog prvog citiranja u tekstu.

Diskusija

U diskusiji se razmatraju dobijeni rezultati. Ta razmatranja se odnose i na ranije publikacije.

U originalnim člancima i kratkim saopštenjima, glavni cilj diskusije je da se odgovori na pitanje koje je postavljeno u uvodu članka. Zato se obično već u prvom pasusu ukratko sumira najvažniji rezultat te studije i navodi glavni odgovor koji iz tih podataka proizlazi. U ovom poglavlju se razmatraju i nedostaci studije (dizajn, broj ispitanika, odgovarajuća kontrola i sl.) koji bi mogli doprinijeti da dobijeni rezultati budu drugačiji od rezultata u ranijim istraživanjima. Tu se navodi i sve ostalo što bi moglo objasniti neujednačenost dobijenih rezultata s podacima iz literature. Zato se definitivni odgovor na pitanje postavljeno u uvodu članka daje tek nakon ovih razmatranja koja sadrže dodatne dokaze koji potkrepljuju prikazane rezultate. Ukoliko je nakon razmatranja činjenica s obje strane nemoguće riješiti konfliktnu situaciju, autori mogu predložiti kojim bi se dodatnim istraživanjima eventualno moglo doći do rješenja.

Zahvalnost

Zahvalnost se piše na kraju tekstualnog dijela rukopisa, prije poglavlja Reference. U tom veoma kratkom poglavlju se autori najčešće zahvaljuju instituciji koja je finansirala istraživanje i onim osobama koje su značajno doprinijele realizaciji istraživanja, a ne postoji opravdanje za njihovo uključivanje među autore. Pri uključivanju osobe u ovo poglavlje, neophodna je njena pismena saglasnost.

Reference

Literatura se u tekstu obilježava arapskim brojevima koji se ispisuju kao *superscript*. Reference dobijaju brojeve po redoslijedu pojavljivanja u tekstu, tabelama i legendama i tim redom one budu ispisane u poglavlju Reference. Ne treba

stavljati tačku ili zarez iza brojeva već ispred. Sve reference za članke na engleskom se pišu na tom jeziku. Ako su radovi objavljeni na nekom drugom jeziku, naslov se ispisuje na engleskom, a na kraju reference u zagradi se navede naziv tog jezika. Reference radova koji su prihvaćeni za štampu se navode uz dodatak "u štampi", a rukopisi predati u štampu, koji nisu prihvaćeni, budu citirani u tekstu tako što se u zagradi navede "neobjavljeni podaci". Ne prihvata se citiranje apstrakta s naučnih skupova, doktorskih disertacija i drugih nepublikovanih dokumenata.

Reference se ispisuju prema preporuci datoj od strane tzv. Vankuverske grupe (www.nlm.nih.gov/bsd/uniform_requirements.html). Standardne skraćenice časopisa mogu se naći na sajtu *PubMed*.

Primjeri

De Lacey G, Record C, Wade J. How accurate are quotations and references in medical journals. BMJ 1985; 291: 884-6.

Dragojević-Simić V, Stojiljković MP, Stanulović M, Boskovic B, Jankovic SM, Milovanovic D. Clinical pharmacology in Serbia: the time for new challenges. Vojnosanit Pregl 2007; 64: 257-63. [In Serbian]

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Croat Med J 2003; 44: 770-83.

Huth EJ. How to write and publish papers in the medical sciences. Philadelphia: ISI Press, 1982.

Davidović L, Marković M, Colić M, Ilić N, Koncar I, Svetković S, Sindjelić R, Marković D. Treatment of traumatic rupture of the thoracic aorta. Srp Arh Celok Lek 2008; 136: 498-504. [n Serbian]

Kažić T, Ostojić M, editors. Clinical cardiovascular pharmacology, Fifth edition. Beograd: Integra, 2009. [n Serbian]

Curtis MJ, Shattock MJ. The role of the manuscript assessor. In: Hall GM, editor. How to write a paper. London: BMJ Publishing Group; 1994, pp 89-95.

Primeri citiranja elektronskih publikacija i upucivanje na Internet "sites":

International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info/Accessibility Verified September 20, 2010.

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfield.libraryupenn.edu/essays/v13p019y1990.pdf. Accessed May 25, 2010.

Wong DN, Vulic BD, Sobot M. Implementation of secondary prevention methodologies in ischemic heart disease. Scr Med 2010;41:29-35. Available at: http://www.scriptamedica.com. Accessed October 1, 2010.

Članci o originalnim istraživanjima ne treba da budu duži od 3000 riječi, uz maksimalno 5 tabela ili ilustracija. Pregledne članke uredništvo prima samo ukoliko jedan od autora navođenjem više od 5 auto-citata u recenziranim časopisima pokaže da je kompetentan za tu oblast. Pregledni članak ne treba da ima više od 3500 riječi s maksimalno dvije tabele i ne više od 60 referenci. Specijalni članci se odnose na sve aspekte medicine i zdravstva, a pišu se na do 3000 riječi uz najviše 5 tabela ili ilustracija.

Pismo uredniku ne treba da bude duže od 200 riječi s maksimalno 5 referenci, jednom tabelom ili jednom ilustracijom. Prednost imaju pisma koja sadrže primjedbe na članak objavljen u prethodnom broju časopisa. Po potrebi, pisma se recenziraju od strane spoljašnjih recenzenata. Sva pisma se šalju autorima na čiji se rad odnose, bez obzira na to hoće li biti objavljena ili ne. Tekstualni dio prikaza slučajeva, bez referenci i tabele, smije da sadrži do 700 riječi. Slike iz kliničke medicine (Images in Clinical Medicine) moraju biti odličnog kvaliteta i popraćene tekstom do 250 riječi.

U prikazu knjige treba da se procijeni njena vrijednost. Zato već u prvom pasusu slijedi odgovor na seriju pitanja. Da li je ta knjiga potrebna? U čemu se razlikuje i da li je bolja od postojećih? Kome je namijenjena i da li je napisana baš za tu kategoriju čitalaca? Zašto se ona svidjela autoru prikaza? U drugom, a eventualno i u dodatnim pasusima, iznosi se sve što se odnosi na kvalitet i namjenu knjige, a u posljednjem pasusu se iznosi zaključak s odgovarajućom ocjenom i preporukom. Ukupan boroj riječi prikaza knjige treba da je manji od 300.

Tabele

Tabele se mogu korisiti za opis odlika grupa u poglavlju "Materijal i metode", a najčešće budu korištene za prikaz rezultata. U tabelu ne treba unositi vertikalne linije. Horizontalne linije se koriste samo za odvajanje naslova i za razdvajanje pojedinih sekcija tabele. (Ukoliko kompjuterski program postavi nepotrebne linije, treba ih izbrisati.) Tabele se označavaju arapskim brojevima redoslijedom pojavljivanja (Tabela 1, Tabela 2 itd) i svakoj se daje naslov. Dodatna objašnjenja se mogu napisati ispod naslova i taj tekst se ispisuje manjom veličnom slova, a ako se objašnjenja daju u fusnoti, onda se za njih koriste simboli: *, ¶, §, €, £, ¥. Svaka tabela mora da se pomene na odgovarajućem mjestu u tekstu. Ako se u tabeli koriste tuđi podaci, obavezno se moraju citirati kao i svaki drugi podatak iz literature. Tabele se prilažu odvojeno od tekstualnog dijela rukopisa.

Tabele treba pisati s dvostrukim proredom na posebnoj strani. Svaka tabela mora posjedovati kratak naslov. Objašnjenja treba staviti u fusnotu, a ne u zaglavlje tabele. Skraćenice treba navesti u fusnoti svake tabele. Svaku tabelu treba citirati u tekstu redoslijedom pojavljivanja.

Ilustracije
Svi oblici grafičkih priloga nose naziv slike. Ilustracije se šalju u posebnom fajlu (GIF ili TIF verzija). Sve oznake na slici treba da su tolike veličine da nakon umanjenja budu čitljive. Naslov i objašnjenje ilustracije (figure legend) treba da bude sastavni dio "word" dokumenta koji se šalje priložen uz "file" s ilustracijama.

Slike se numerišu arapskim brojevima prema redoslijedu citiranja u tekstu. Njih treba profesionalno izraditi. Umjesto originalnih crteža, rendgen filmova i drugog materijala, mogu se izraditi fotografije. Simbole, strelice, brojeve ili slova kojima se označavaju dijelovi ilustracija treba objasniti u legendi. Internu skalu treba objasniti i navesti metod bojenja mikroskopskih uzoraka.

Skraćenice i simboli
Skraćenice ne treba koristiti u naslovu i apstraktu. Standardne skraćenice se mogu koristiti u tekstu, a sve ostale se načine tako što se iza punog naziva kod prvog pominjanja u zagradi daje skraćenica.

Jezik i stil
Tekst originalnih saopštenja, preglednih članaka, prikaza slučajeva i uvodnika piše se latinicom, a ostali članci ćirilicom ili latinicom na ekavskom ili ijekavskom narječju. Prošlo vrijeme se koristi kada se saopštavaju dobijeni rezultati, a sadašnje vrijeme za prikaz publikovanih radova. Otuda većina teksta u poglavljima apstrakt, metode i rezultati budu pisani u prošlom vremenu, a sadašnje vrijeme se koristi kada se pišu zaključci. Duge rečenice otežavaju čitanje, a ponekad i razumijevanje poruke. *Scripta Medica* ne prihvata pasuse koji sadrže samo jednu rečenicu. Glagole je najbolje upotrebljavati u aktivu. Pri sastavljanju rukopisa, autori treba da imaju na umu da pišu članak koji je namijenjen čitaocima s opštim medicinskim znanjem.

Autorstvo, integritet istraživača, konflikt interesa i etički standardi
Vankuverska grupa je ukazala da koautor članka može biti ona osoba koja je dala "značajan" doprinos istraživanju. Zato se od svakog koautora rukopisa koji se šalje u SM traži da je učestvovao u radu u mjeri koja ga obavezuje na odgovornost prema naučnoj i stručnoj javnosti za odgovarajući dio u izvođenju istraživanja i izrade rukopisa. To uključuje: (1) koncept i dizajn istraživanja ili prikupljanje podataka, te njihovu analizu i interpretaciju; (2) pisanje prve verzije ili vršenje revizije rukopisa; i (3) prihvatanje finalne verzije koja se šalje u SM. Saradnici ne treba da uredništvu prilažu opis svojih poslova, jer glavni autor (garant) uzima na sebe odgovornost za integritet članka i autorstva. Ostali saradnici koji su doprinijeli radu, a ne ispunjavaju uslove za autorstvo, mogu se pomenuti u 'Zahvalnosti' s tim da se naznači u čemu je bio njihov doprinos.

Plagijatizam, falsifikovanje i izmišljanje podataka su najteži oblici kršenja integriteta istraživača. Takve pojave se ponekad dešavaju, ali se one veoma često otkrivaju prije ili poslije publikovanja članka.

Autori su dužni da saopšte redakciji finansijsku vezu autora sa industrijom (na primjer, konsultacije, honorari, posjedovanje akcija i sl.). Uredništvo će procijeniti koliki je potencijalni uticaj takve veze i ukoliko postoji značajniji konflikt interesa, isti će biti objavljen na kraju članka.

Na početku poglavlja "Materijal i metode" se za eksperimente na ljudima ili životinjama mora navesti da su odobreni od strane odgovarajućeg etičkog odbora ustanove (EOU), a za eksperimente na ljudima se mora naznačiti i da su učesnici dali pismenu saglasnost (informed consent). Urednik može od autora zatražiti kopiju odobrenog zahtjeva EOU.

Pisanje materijala za sredstva javnog informisanja ("press release")
Informaciju namijenjenu široj javnosti pišu autori na 150 do 250 riječi kada to predloži uredništvo. Rečenice treba da budu kratke, a izrazi razumljivi širokoj publici. Tehničke termine treba pri prvom pominjanju objasniti. Na kraju teksta, navodi se ime autora koji je zadužen za kontakt s medijima, njegova adresa, telefon i e-adresa. Autorima je zabranjeno davati direktne informacije novinarima prije nego što se skine embargo, tj. iste se mogu dati tek nakon objavljivanja rada u časopisu.

Instructions for Contributors

Scripta Medica is a peer-reviewed international journal published under the auspices of the Medical Society of the Republic of Srpska. The journal will publish original biomedical studies, including ethical and social issues. *Scripta Medica* gives preferences to clinically oriented studies over those with experimental animals and will publish peer-reviewed original research papers, case reports systematic reviews, medical history and educational essays, clinical mages, book reviews, letters to the editor and editorials. The journal's full text is available, free of charge, online at www.scriptamedica.com.

Each contributor should participate in one or more of the following aspects of an original article: (1) the concept and design of the study; (2) acquisition of data, its analysis and interpretation; (3) drafting and critical revision; (4) final approval of the version to be published. The senior-corresponding author is responsible for the integrity of the work as a whole. The corresponding author must provide a Cover letter indicating that all authors agree to the contents of the submitted paper. Conflict of interest must also be provided.

These instructions are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (www.icmje.org).

Manuscripts deemed suitable for publication by in-house assessment will be reviewed by two or more outside experts. Contributors are encouraged to provide names of two or more qualified reviewers with experience in the subject of the submitted manuscript, but this is not mandatory. Page proofs of accepted articles will be sent to the corresponding author, and the corrected proofs should be returned within three days. The entire process, from submission of the manuscript to the final review, including the sending and receiving of page proofs can be completed online.

Technical Requirements

The journal will review manuscripts submitted to:
editor@scriptamedica.com

For the text one should use word format, and for the illustrations JPG or TIFF format.

Manuscripts of Original Research

Manuscripts that describe clinical or laboratory investigations may be no longer than 3000 words, excluding abstract, tables, and references. Each manuscript should contain following sections:

a) *Title page*. The title page contains the title of the article, the full name of each author, the name of the department(s) and institution(s) to which the work should be attributed, disclaimers (if any), name and address of the corresponding author, and a short running title of no more than 40 characters, including spaces.

b) *Abstract and Key Words*. When required, provide an Abstract of no more than 250 words. It should contain four labeled paragraphs: Background, Methods, Results, and Conclusions. Conclusions should emphasize new and important aspects of the study or original observations. Below the abstract authors should provide 3-8 key words or short phrases. Use terms from the Medical Subject Headings from *Index Medicus*. Review articles and Special articles (only history) require a 150 words, single paragraph (not structured) abstract. Case reports need no Abstract.

c*) Introduction*. This section includes the purpose of the study and summarizes the rationale for doing it, using only relevant references.

d*) Materials and Methods*. Clearly describes selection of observational or experimental subjects (patients, laboratory animals, tissue samples or cell lines) and relevant controls. Indicate age, sex, and other important characteristics of the subjects. Manuscripts describing investigations using humans or animals must confirm approval of the study by an Institutional Review Board. Identify all methods, apparatus (manufacturer's name and location in parentheses), and describe procedures in sufficient detail to allow others to reproduce them. Measurements of distance, length, and weight are to be expressed in metric units. Laboratory, hematological, and clinical data should be expressed in SI units, with conventional metric units indicated in parentheses. Reference all established methods, including statistical analyses. Identify all drugs and chemicals used, including generic names, doses, and routes of administration. Statistical methods should be described such that a reader with access to the original data could verify the reported results. Variability should be expressed in terms of means and standard deviations (SD), not the standard error of the mean (SEM). Because SD and SEM are positive numbers, the Council of Science Editors (Reston, 2006) recommends elimination of a +/- sign; instead, the SD is given in brackets. For example, "systolic blood pressure in group of healthy students was 129 mm Hg [SD = 6, n = 87]."

Authors submitting review manuscripts should describe the methods used to locate, select, extract, and synthesize data. These methods should also be summarized in the abstract.

e) *Results.* Results should be presented in logical sequence using the text, tables, and illustrations. Do not repeat data presented in tables or illustrations in the text. Emphasize or summarize only important observations.

f) *Discussion.* Emphasize the new and important aspects of the study and the conclusions that follow from them. Discuss the implications of the findings and their limitations. Significant findings should be related to other relevant studies, and conclusions should be linked to the goals of the study. Do not repeat data or summarize material from the Introduction or the Results sections.

g) *Acknowledgments.* List all contributors who helped, even if they did not meet the criteria for authorship as well as financial and material supporters.

h) *References.* References should be numbered consecutively with Arabic numerals (superscripts) in the order in which they first mentioned in the text, tables, and legends. References cited only in tables or figure legends should be numbered in accordance with the sequence established by their first mention in the text or figure or table. Titles of journals are to be abbreviated according to the *Index Medicus*. All titles of should be in English with the original language in brackets. Examples given here conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org):

De Lacey G, Record C, Wade J. How accurate are quotations and references in medical journals. BMJ 1985; 291: 884-6.

Dragojević-Simić V, Stojiljković MP, Stanulović M, Boskovic B, Jankovic SM, Milovanovic D. Clinical pharmacology in Serbia: the time for new challenges. Vojnosanit Pregl 2007; 64: 257-63. [In Serbian]

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Croat Med J 2003; 44: 770-83.

Huth EJ. How to write and publish papers in the medical sciences. Philadelphia: ISI Press, 1982.

Davidović L, Marković M, Colić M, Ilić N, Koncar I, Svetković S, Sindjelić R, Marković D. Treatment of traumatic rupture of the thoracic aorta. Srp Arh Celok Lek 2008; 136: 498-504. [In Serbian]

Kažić T, Ostojić M, editors. Clinical cardiovascular pharmacology, Fifth edition. Beograd: Integra, 2009. [In Serbian]

Curtis MJ, Shattock MJ. The role of the manuscript assessor. In: Hall GM, editor. How to write a paper. London: BMJ Publishing Group; 1994, pp 89-95.

Electronic publications:
International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info/Accessibility Verified September 20, 2010.

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfield.libraryupenn.edu/essays/v13p019y1990.pdf. Accessed May 25, 2010.

Wong DN, Vulic BD, Sobot M. Implementation of secondary prevention methodologies in ischemic heart disease. Scr Med 2010;41:29-35. Available at: http://www.scriptamedica.com. Accessed October 1, 2010.

Tables
Tables (maximum 4) should be self-explanatory and numbered in Arabic numerals in order of their mention in the text. Type each table, double-spaced, on a separate sheet and supply a brief title. Place any explanatory text in footnotes, not in the heading. Define abbreviations in footnotes.

Illustrations (Figures)
Figures should be professionally drawn and numbered with Arabic numerals in the order of their mention in the text (maximum 2). All lettering should be dark against a white background and of sufficient size to be legible when reduced for publication. Do not send original artwork, x-ray films, or ECG tracings but rather photographs of such material. Color images need to be at least 300 DPI. Figure legends should be typed double-spaced on a separate page with Arabic numerals corresponding to the figure. All symbols, arrows, numbers, or letters should be explained in the legend. Photomicrographs should include an internal scale, and methods of staining should be described in the legend.

Review Articles
Review articles are written by individuals who have worked sufficiently in a particular area to be considered experts. Word count is limited to 3500 words or less, excluding tables (maximum 4), references and abstract. The manuscript may have as many as 50 references.

Case Reports
New, interesting, or rare cases can be reported in communications no longer than 700 words. They should include the following: *Introduction, Case Presentation, Discussion, and up to six References*. Up to three illustrations is permitted. Case reports could be authored by up to five authors.

Images in Clinical Medicine
The editors will consider original, high quality images showing novel or "classic" findings for publication. All submissions should be accompanied by a cover letter as well as a concise description of no more tan 250 words including the title page and references.

Clinical Problem-Solving
Solution for various clinical problems, including certain clinical studies, should include the following: Introduction, Methods or Case(s) Presentation, Discussion, and References. Four tables or illustrations. This communication should be no longer than 1400 words, including references and tables.

Letter to the Editor
If in reference to a recent journal article, letters are limited to 150 words, excluding references, or 200 words in all other cases. The letter should contain no more than five references, and may include one figure or table. Please include your full address, phone number, fax number, and an e-mail address.

Editorials
Editorials are solicited by the Editorial Board to provide editorial perspective on articles published in the journal and/or express the general policies or opinions of the Editorial Board.

Special Articles
Articles that do not readily fall into the above categories may be published as Special Articles (e.g., history, education, demography, contemporary issues, etc). Word count is limited to 3000 words for history articles or educational articles with up to 6 tables or illustrations. Other Special articles may have up to 1000 words. Only history articles need Abstract (unstructured).

Conflict of Interest
Authors of research articles should disclose at the time of submission any financial arrangement they may have with a company whose product figures prominently in the submitted manuscript. Such information will be held in confidence while the paper is under review; if it is accepted for publication, the editors will discuss with the author how such information will be communicated to the reader.

Review Procedure
At least two members of the editorial board initially evaluate all submissions for originality, relevance, statistical methods, significance, adequacy of documentation, reader interest, and composition. Articles that do not conform to the journal instructions will be returned to the authors. Manuscripts suitable for peer review will be sent to two outside reviewers, who then have up to a month to provide their reviews. The ultimate authority to accept or reject an article rests with the Editor. Revised manuscripts may be accepted depending upon the adequacy of responses to suggestions and criticisms during the initial review. A letter to the principal author will communicate acceptance of the manuscript.