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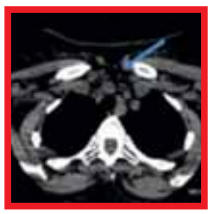

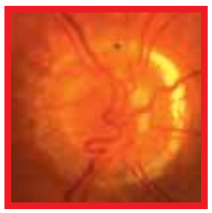

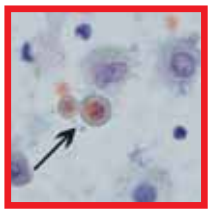

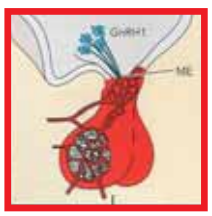

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Садржај / Contents

У овом броју/*In This Issue*

У првом овогодишњем броју часопис *Scripta Medica* објављује оригинална истраживања, приказе случајева, писма уреднику, специјалан стручни чланак, едукативни прилог Questions & Answers, чланак о рецензирању и друге прилоге.

Резултати фармакоепидемиолошке студије (Марковић-Пековић В. и сар.) – праћена је ванболничка употреба антибиотика у Републици Српској у периоду од 2007. до 2011. године – показали су да је коришћење антибиотика код нас слично оном у развијенијим европским земљама. Међутим, имајући у виду брз пораст бактеријске резистенције, употреба антибиотика, и код нас и у свету, мора бити још опрезнија. Прилог из неурологије (Драча С.) односи се на утицај пола и латерализације на тежину постапоплектичне депресивне симптоматологије. Важан прилог из офталмологије посвећен је лечењу кератоконуса (Epstein R. L. and Epstein G. L.).

Леп приказ случаја из офталмологије (Маркић Б. и сар.) односи се на ретку аномалију оптичког диска. Други је клинички случај (Voronov D., et al) интересантан и за лекаре и стоматологе. Реч је о супкутаном емфизему који је захватио и медијастинум, а појавио се након рутинске стоматолошке интервенције – ‚пломбирања' левог максиларног моларног зуба. Кратак приказ 57-годишњег мушког болесника, који је због смањеног имунитета услед карцинома надбубрежне жлезде и његове метастазе у плућима имао двоструку плућну инфекцију (Blastomyces/Pleumocystis jiroveci), објавила је патолог (Bero J. L.).

Специјални чланак (Антонијевић Н. М. и сар.) посвећен је клиничкој пракси; односи се на факторе ризика у настанку венске тромбоемболије и трајање антикоагулантне терапије. Едукативне прилоге под називом Q & A објављујемо за читаоце који слабије познају енглески језик. Да би ово штиво било многима интересантије, чак и онима који добро познају тај језик, аутори (Мавија М. и сар.) су изабрали питања из разних биомедицинских области и дали одговоре.

У овом свеску *SM* објављују три писма уреднику. Та су нам писма упућена из Енглеске, Чешке и САД, а односе се на чланке који су објављени у претходним бројевима нашег часописа. Многи нам читаоци захваљују што смо увели ту рубрику; наводе да у новом броју најпре потраже та писма. Можда је чар ових прилога у томе што тако читаоци комуницирају с ауторима саопштења, али и због тога што су та писма кратка, језгровита и интересантна.

У овом броју објављујемо списак Публикација из Републике Српске у часописима уврштеним у Medline и корекције Упутства ауторима (на српском и енглеском језику).

На крају треба поменути да је у овом броју *SM* објављен чланак-упутство о рецензирању рукописа. Тај прилог је вредан пажње не само оних који рецензирају рукописе, него и аутора научних саопштења.

Scripta Medica

UDK 615.03:613.2-099

EDITORIAL

Case Reports and Adverse Drug Reactions

Case reports—descriptions of one or more patients—used to be the most common type of publication in medical journals. Today only some journals accept case reports; these include open access journals, for example the *Journal of Medical Case Reports*. Such contributions generally illustrate some novel clinical problem or its solution.[1] Case reports are most likely to be published if they describe any of the following: 1) an unreported adverse drug reaction or interaction, 2) a new, unexpected, or unusual pattern of a disease, 3) previously unsuspected causal association between two diseases, 4) presentations, diagnosis and/or management of new and emerging diseases, 5) an unexpected association between diseases or symptoms, 6) an unexpected event in the course of observing or treating a patient, 7) findings that shed new light on the pathogenesis of a disease or an adverse effect or diagnosis, and 8) a previously unknown disease. (The unknown disease may happen quite rarely.)

In the hierarchy of evidence-based medicine, single case reports remain at the very bottom.[2] However, even a single case report can stimulate further confirmatory investigations, especially if the report goes beyond cursory observation. For example, a report of an increased incidence of leukemia within a single neighborhood can contribute to the defining characteristics of what may be an evolving disease cluster.[3]

Case reports on suspected adverse drug reaction (ADR) could also inspire subsequent systematic research that will ultimately contribute to the evidence based medicine. Any suspected ADR needs to be confirmed or refuted. Often suspected, new adverse drug reactions remain unverified; in fact, at least two reports indicate that from 26%[4] to 83%[5] of ADRs are not confirmed. Many published reports of suspected ADR are thus of limited value, because these signals are seldom investigated further. Furthermore, because this information is not incorporated consistently into drug reference sources, physicians and patients remain unaware of the potential adverse effects.[6]

In 1971, an international system for monitoring ADRs was established (WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Sweden). The database in Uppsala currently contains over three million reports of suspected ADRs. These reports use common terminologies and classifications and are supplied by physicians, qualified nurses, and pharmacists.[7] This extensive system for voluntary reporting of ADRs has a quantitative advantage (especially if patient reports are included[8]) over the case reports of ADRs published in journals, yet the case reports provide a better quality of information.

Scripta Medica publishes case reports, including those on adverse drug interactions, as well as review articles on this subject.[9] Short description of a case that would not make a full-length paper may be published as a letter to the editor. Our journal accepts these contributions as well, so long as the letter is brief and to the point.[10] The main purpose of case reports on ADRs is to stimulate vigilance and debate on this important subject.

ADRs are frequently used as examples to provide practical advanced courses in clinical pharmacology and therapeutics. The ADR case,[11] of diffuse myopathy presented here was used to stimulate discussion on drug interactions.

An 83-year-old woman presented to our clinic with a chief complaint of progressive immobilizing myopathy starting a week ago. The patient also complained of lower back pain and revealed that her urine output had sharply decreased. This patient had a history of hypercholesterolemia and had taken simvastatin (20 mg once a day) for one year. She also had hypertension and was treated with a calcium channel blocker, amlodipine (5 mg four times daily) for ten months. Because she developed edema in her lower extremities, a loop diuretic, torasemide (5 mg once daily), was added. After six months her blood pressure remained at 180/90 mmHg, so her antihypertensive therapy was changed to mibefradil[1] (50 mg once daily) one month prior to her admission. Three weeks after the change to mibefradil, the patent began experiencing muscle pain and gait disturbances. Although she has taken NSAIDs for several days, her problems have persisted.*

At the physical exam, it was found that she was unable to walk due to "functional disability" of her legs. She had a diffuse myopathy with suppressed deep-tendon reflexes. Her blood pressure was 150/80, and she had a normal body temperature. The lab data were as follows: ALT 1.179 U/L, AST 988 U/L, phosphorus 2.45 nmol/L, creatine kinase 50.125 U/ml, potassium 7,2 mmol/L, serum creatinine 814 micromol/L, urea 46,1 mmol/l]L, with myoglo-

[1] In 1998, Roche voluntarily withdraw mibefradil from the market because of its potentially harmful interactions with various drugs, especially statins. Pravastatin has a neutral drug interaction profile relative to cytochrome P450(CYP)-3A4 inhibitors (mibefradil, verapamil, itraconazole, bergamottin), but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. Bergamottin, the primary furanocoumarin extracted from grapefruit juice, inhibits CYP-3A4 in liver microsomes and increases bioavailability of various drugs; a few deaths due to such food-drug interactions have been reported. Use of grapefruit during therapy with drugs that are metabolized by CYP-3A4 should be avoided.

binuria. Serum sodium, calcium and GGT were normal, and tests for HIV, hepatitis B and hepatitis C were negative. Serum levels of simvastatin and its metabolite beta-hydroxy-simvastatin acid, measured 24 hours after the last dose, were 4.95 and 1.02 ng/ml, respectively.

The following questions related to this ADR case may be discussed with students or residents: 1) What is the cause of this adverse event? and 2) How could this adverse event have been prevented? To facilitate discussion, the students and residents should read several papers, including those given in the list of references.[9-15]

In conclusion, case reports may illustrate novel clinical problems and/or their solutions. These reports are published in the medical journals. However, case reports that make some important teaching point of what is already well known but often forgotten, are now rarely published in medical journals. Instead, such contributions sometimes appear as a Letter to the Editor or among the Images in Clinical Medicine journal section. An Interesting case report, especially if it is related to the ADR, can be used as teaching material, and it may be published in the manuals or handbooks of clinical pharmacology and therapeutics.[16]

Rajko Igić
Nataša Stojaković

References

1. Fraser J. *How to publish in biomedicine—500 tips for success*, second edition. Oxford, Radcliffe Publishing, 2008.
2. Igić R, Škrbić R. *Kako se pišu i publikuju biomedicinska naučna saopštenja*. Banja Luka/Laktaši, GrafoMark, 2012.
3. Taylor RB. *The clinician's guide to medical writing*. New York, Springer, 2005.
4. Loke YK, Price D, Derry D, Aronson JK. Case reports of suspected adverse drug reactions—systematic literature survey of follow-up. *BMJ* 2006;332:5.
5. Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. *BMJ* 1982;284:249-52.
6. Loke YK. Assessing the benefit-harm balance at the bedside. *BMJ* 2004;7-8.
7. Ulfarson J, Mejyr S, Bergman U. Nurses are increasingly involved in pharmacovigilance in Sweden. *Pharmacoepidemiol Drug Saf* 2007;16:532-7.
8. Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess* 2011;15:1-234.
9. Kažić T. Statini—neželjena dejstva i interakcije. *Scr Med* 2011; 42:132-9.
10. Ljubojević G, Tomić N, Stojaković N. Statin-induced leg pain at night. *Scr Med* 2011;42:110.
11. Stojaković N, Igić R. Simvastatin-induced leg pain disapperas with pravastatin substitution. Srp Arh 2013 (in press).
12. Ratain M, Shepard D. Adverse drug reactions. In: *Advanced clinical pharmacology and therapeutic*s, course syllabus. Chicago, University of Chicago, 1999.
13. Jacobson RH, Wang P, Glueck CJ. *JAMA* 1997;277:296. doi:10.1001
14. Po AL, Zhang WY. What lessons can be learnt from withdrawal of mibefadil from market? *Lancet* 1998;351:1829-930.
15. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
16. Igic R. *Praktikum iz farmakologije, toksikologije i kliničke farmakologije*. Tuzla, Medicinski fakultet, 1988.

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ORIGINAL ARTICLE

Outpatient Utilization of Systemic Antibiotics in the Republic of Srpska

***Vanda Marković Peković*[1]**
***Svjetlana Stoisavljević-Šatara*[2]**
***Ranko Škrbić*[2]**

[1]*Ministry of Health and Social Welfare*
[2]*Department of Pharmacology and Toxicology*
School of Medicine
University of Banja Luka
Banja Luka, Republic of Srpska
Bosnia and Herzegovina

Correspondence
Vanda Marković Peković
Ministry of Health and Social Welfar
Trg Republike Srpske
78 000 Banja Luka
Republic of Srpska
Bosnia and Herzegovina
Tel + 51 339 427
e-mail:
v.mpekovic@mzsz.vladars.net

ABSTRACT

Introduction. Information on antibiotic utilization in the Republic of Srpska is limited. The aim of this study was to analyze antibiotic utilization in the community from 2007 to 2011 and to compare this data with antibiotic use in other European countries.

Materials and Methods. We did a population-based study to analyze systemic antibiotic utilization by an outpatient population using Anatomical Therapeutic Chemical/Defined Daily Dose methodology. The results were expressed as the defined daily dose (DDD) per 1000 inhabitants per day. The data were obtained from the annual reports of the Agency for Drugs and Medical Devices of the Republic of Srpska and Public Health Institute.

Results. Outpatient use of systemic antibiotics ranged between 21.51 DDD in the year with the highest use (2010) and 17.01 DDD in the year with the lowest use (2011). Penicillins were the most frequently prescribed antibiotic group, and amoxicillin was the most frequently prescribed drug. Cefalexin was the most frequently prescribed cephalosporin. Increased use of a second-generation cephalosporin, cefuroxime constituted almost a third of cefalexin consumption in 2011. Second-generation quinolones, mostly ciprofloxacine, accounted for about 70% of total quinolones consumption, with rising third-generation drugs also in proportion to the increasing use. Erythromycine was the most frequently used macrolide, followed by long-acting azithomycin.

Conclusion. Outpatient use of systemic antibiotics in the Republic of Srpska, at about 19 DDD, does not exceed that in Europe. As in other European countries, a shift between generations of drugs was noted for antibiotic use. Additional studies, including monitoring of seasonal variation impact on antibiotic use, are needed.

KEY WORDS

Antibiotics, drug utilization, outpatient care, pharmacoepidemiology.

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The overuse of antibiotics is the main force driving increased bacterial resistance, which poses a major threat to public health.[1,2] The vast majority of human antibiotic utilization occurs within the community,[3,4] where as much as 20 to 50% of antibiotic use may be questionable.[5] Although antibiotics are prescription-only medicines, their use may also include self-medication.[6,7] In addition to higher rates of antimicrobial resistance, the consequences of antibiotic overuse and misuse include the risk of adverse side effects and higher costs.[8,9] Cost-effectiveness studies on antibiotic therapy now consider the influence of bacterial resistance.[10] In order to assess the extent of the problem, it is necessary to collect and analyze data on antimicrobial prescribing in different clinical settings.

The number of antibiotic prescriptions has remained fairly stable in recent years,[11] but prescribing practices and outpatient antibiotic utilization vary widely across Europe.[12,13] Data on the prevalence of resistance in human pathogens show geographic differences in resistance to various classes of antibiotics in Europe. For example, resistance remains low in northern European countries.[3,14] Countries with the highest per capita antibiotic utilization have the highest resistance.[15]

Southern and Eastern European countries are recognized as high antibiotic-consuming countries with increasing use by outpatients.[3,11,16] Taking these findings into consideration along with its geographical location in Southeastern Europe, we assumed that the Republic of Srpska might have a high rate of antibiotic utilization compared with other European countries. However, information on outpatient antibiotic utilization in the Republic of Srpska is limited.[17,7]

The aim of this study is to measure and analyze the utilization of systemic antibiotics in the Republic of Srpska from 2007 to 2011 and to compare these data with those from other European countries.

Materials and Methods

A retrospective, observational, population-based study analyzed antibiotic utilization in the Republic of Srpska during the 5-year period from 2007 through 2011. The analysis covered antibacterials for systemic use (class J01, according to Anatomical Therapeutic Chemical (ATC) classification), excluding antifungals, antibacterials for tuberculosis, antitumoral and topical antibiotics. By legislation, antibiotics for systemic use are prescription-only medicines prescribed by a physician and dispensed by a pharmacist; they are only available in pharmacies.

The data were collected from the annual reports of the Agency for Drugs and Medical Devices of the Republic of Srpska (Agency) for 2007-2008 and Public Health Institute (Institute) for 2009-2011 period. Although the Agency ceased to exist in 2009, data collection procedures were transferred to the Institute. Because of the mandatory annual reporting required of health institutions on drug utilization, the collected data constitute the overall outpatient utilization of antibiotics for systemic use from 2007-2011.

Drug utilization was analyzed using Anatomic Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology, and the results were expressed as the defined daily dose (DDD) per 1000 inhabitants per day (DDD/TID). The ATC system classifies the drugs according to the organ or system on which they act and by their chemical, pharmacological and therapeutic properties. All drugs were classified into ATC groups by their international nonproprietary names (INN). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD/TID is a useful indicator for national and international comparisons, especially when areas to be compared have different numbers of inhabitants. Hereafter, for the purposes of this study, the acronym DDD will indicate DDD/TID. The DDD was calculated according to new DDD values.[18] Although DDDs do not take into account different doses for children and might not adequately address differences in dosage and length of treatment for specific classess of antibiotic between countries,[3] it was confirmed that DDD/TID is an acceptable measurement unit to express and compare outpatient antimicrobial use among countries.[19] Statistics on total population number were taken from Republic of Srpska Institute of Statistics.[20]

Results

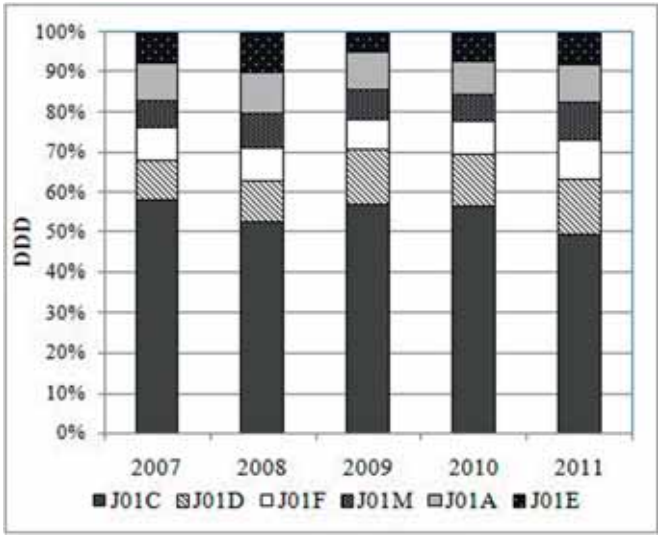
Outpatient antibiotic use varied from 21.51 DDD in the year with a highest use (2010) to 17.01 DDD in the year with the lowest use (2011). Penicillins were the most frequently pre-

Table 1. Yearly outpatient antibiotic use expressed in DDD

INN		2007	2008	2009	2010	2011
J01A	tetracyclines	1,89	1,79	1,85	1,75	1,55
J01C	penicillins	11,58	9,29	10,98	12,12	8,41
J01CA	extended-spectrum	8,56	7,49	9,20	10,15	6,10
J01CE	beta-lactamase-sensitive	2,35	1,38	1,40	1,57	0,98
J01CR	combination of penicillins*	0,64	0,42	0,37	0,39	1,33
J01D	cephalosporins	1,96	1,82	2,64	2,86	2,30
J01DB	first generation	1,51	1,57	2,04	2,16	1,58
J01DC	second generation	0,45	0,24	0,57	0,66	0,68
J01DD	third generation	na	0,01	0,03	0,041	0,040
J01EE	sufonamides & trimethoprim	1,55	1,77	0,92	1,55	1,40
J01F	macrolides and lincosamides	1,67	1,46	1,44	1,72	1,70
J01FA	macrolides	1,67	1,46	1,43	1,71	1,68
J01FF	lincosamides	na	na	0,006	0,007	0,013
J01M	quinolones	1,33	1,57	1,46	1,51	1,64
J01	total	19,98	17,70	19,29	21,51	17,01

INN = International Nonproprietary Name;*combination with β-lactamase inhibitors;
N/A = not applicable, i.e. not on the market

Figure 1. Outpatient use of J01 subgroups, expressed as % of total J01 consumption in DDD



J01C = Penicillins; J01D = Cephalosporins; J01F = Macrolides and lincosamines;
J01M = Quinolones; J01A = Tetracyclines; J01E = Sulfonamides and trimethoprim
DDD = Defined Daily Dose

scribed antibiotics in all years, ranging between 59% (2007) and 49,4% (2011), followed by cephalosporins, which ranged from 13,5% (2011) to 9,8% (2007) for total outpatient antibiotic use. The proportion of macrolides within the total antibiotic use ranged from 10,0% (2011) to 7,5% (2009); quinolones ranged from 9,6% (2011) to 6,7% (2007, and tetracyclines ranged from 10,1% (2008) to 8,1% (2010). Sulfonamides and trimethoprim were solely represented by sulfomethoxazole with trimethoprim, and their use varied from 8,2% (2011) to 4,8% (2009) (Table 1, Figure 1).

Narrow-spectrum penicillins (NSP, J01CE) represented 14,5% of total antibiotic use, broad-spectrum penicillins (BSP, J01CA) 78,9% and combinations of penicillins with β-lactamase inhibitor (COP, J01CR) made up 6,6% of total outpatient penicillin use (Table 1). Benzathine phenoxymethylpenicillin was the most used NSP with 11,2% of the total penicillin utilization by 2011 (1.4 DDD 2007; 1.0 DDD 2010; 0.2 DDD 2011), followed by phenoxymethylpenicillin, where we noted considerable fluctuations in use (Table 2). Amoxicillin was the most used BSP (Table 2). The proportion of amoxicillin in total penicillin use was the form given with an enzyme-inhibitor (co-amoxicillin); this figure increased from 3,2% (2010) to 15,8% (2011) (Table 2). First-generation cephalosporins, namely cefalexin, represented 77% of the total use of that drug class. Second-generation cephalosporins contributed 22,1%, and third-generation drugs contributed 0,9% (Table 1). Cefuroxime was the most prescribed second-generation cephalosporin (Table 2), followed by cefaclor (0.2 DDD 2007; 0.1 DDD 2011).

Second-generation quinolones accounted for 67,8% of the total drugs in that class, and first-generation quinolones contributed 32,2%, with the rising third generation contributing only a small proportion (0,3% 2009; 1,0% 2011). Utilization of a first-generation quinolone, pipemidic acid, declined continuously from 0.24 DDD in 2007 to 0.17 DDD in 2011, while norfloxacin utilization was approximately 0.3 DDD. Ciprofloxacine was the most prescribed second-generation quinolone with increased consumption over time (Table 2) while ofloxacin use decreased (0.07 DDD 2007; 0.003 DDD 2011). Doxycycline accounted for 93,4% of total outpatient tetracycline use; oxytetracycline and tetracycline use was minor and decreased over time. A short-acting macrolide, erythromycin, was the most prescribed drug of this class, followed by the long-acting azithomycin (Table 2) and an intermediate-acting macrolide clarithromycin (0.2 DDD 2007; 0.4 DDD 2011). Table 2 shows the ten most commonly prescribed antibiotics during the period observed in this study.

Discussion

Total outpatient antibiotic utilization was not as high as expected, based upon reported antibiotic use in Southern and Eastern Europe.[3,12,14] Indeed, our average consumption of 19.1 DDD over the five year period of 2007-2011 is comparable to that in European countries, where an average of 19.9 DDD was reported in 2009.[21] The total outpatient antibiotic utilization in the Republic of Srpska in 2009 was similar to that in countries in our near surroundings, such as Croatia (21.2 DDD) or Bulgaria (18.6 DDD). The moderate use of systemic antibiotics in our country is comparable to that in countries with a long history of low antibiotic utilization, such as the Nordic countries.[22]

In contrast, there were large differences between neighboring Northern European countries. Outpatient antibiotic use in Europe in 2009 differed widely, varying by a factor of 3.5 between the country with the highest (38.6 DDD in Greece) and the lowest (11.1 DDD in Estonia).[21] Unlike the increase noted in most European countries,[16,21] our outpatient antibiotic use remained stable over the five year period of observation. Differences in antibiotic use between countries might be explained by a number of factors, such as variations in incidence of community-acquired infections, culture, education, differences in drug regulation and in the structure of the national pharmaceutical market.[3] Some differences in total outpatient antibiotic use in the European countries were likely influenced by fluctuations in availability of certain antibiotics, e.g., mostly narrow-spectrum penicillins, and the seasonality of outpatient antibiotic use.[3,16,21] Fluctuations in antibiotic availability also occurred in our market, but due to the lack of relevant data, we were unable to evaluate the influence of seasons. Further investigation of such variations may help to identify sources of inefficiency in antibiotic therapy.[12]

Penicillins were the most frequently prescribed antibiotics in the Republic of Srpska and showed an increasing use, similar to other countries. Proportional use of NSP in total penicillin

Table 2. Ten most prescribed antibiotics for systemic use (DDD)

ATC	INN	2007	2008	2009	2010	2011
J01CA04	amoxicillin	7.82	6.64	8.41	9.62	5.72
J01DB01	cefalexin	1.51	1.57	2.04	2.16	1.58
J01AA02	doxycycline	1.66	1.66	1.75	1.67	1.48
J01EE01	sulfamethoxazole and trimethoprim	1.55	1.77	0.92	1.55	1.41
J01CR02	amoxicilline and enyzme inhibitor	0.64	0.42	0.37	0.39	1.33
J01MA02	ciprofloxacin	0.77	1.03	0.94	1.00	1.13
J01CE02	phenoxymethylpenicillin	0.92	0.33	0.37	0.15	0.81
J01FA01	erythromycin	0.99	0.75	0.88	1.10	0.71
J01FA10	azythromycin	0.49	0.45	0.30	0.32	0.59
J01DC02	cefuroxime	0.24	0.06	0.44	0.50	0.56

ATC = Anatomic Therapeutic Chemical; INN = International Nonproprietary Name;
DDD = Defined Daily Dose

utilization was considerably less than that in Nordic countries (50%) but much higher than in France, Greece, Spain and Belgium (<5%).[16,23] We prescribed benzatin phenoxymethylpenicillin more often than phenoxymethylpenicillin, as did Austria, Croatia and the Czech Republic but not the Nordic countries.[23] Both of these NSP were reimbursed. Amoxicillin was the most prescribed of all penicillins, accounting for about 70% of total outpatient penicillin utilization. It was used far more than ampicillin, which is almost entirely superseded by amoxicillin in most European coutries.[23] Continuous decline in ampicillin use was also noted in our study. Amoxicillin utilization declined by 40% in 2011 followed with a 3.5 times increase in the use of co-amoxiclav (Table 2). Versporten et al. reported that BSP (mainly amoxicillin) use decreased in favor of COP in most countries participating in the European Surveillance of Antimicrobial Consumption (ESAC) project, where co-amoxiclav use reached 7 to 10 DDD in the high-consuming countries.[23] This finding raises concern regarding the appropriate prescribing of co-amoxiclav for respiratory tract infections, which are one of the main reasons that antibiotics are prescribed in outpatients.[24] Our co-amoxiclav utilization is still comparable to that of the low-consuming countries (Denmark, Finland),[25,26] but close monitoring of COP utilization is needed especially because one more amoxicillin combination (with sulbactam) became available in 2011.

Cefalexin was the most prescribed cephalosporin, mostly because it has been the only reimbursable cephaloporin for years. Predominant prescribing of a first-generation cephalosporin was reported as well in Finland, Sweden and Iceland, but since 1997, cefalexin use decreased while most countries recorded proportionate increases in second- and third-generation cephalosporins, mostly cefuroxime.[27] Increased utilization of oral cefuroxime (second-generation) and cefixime (third-generation) was also noted in our study. Cephalosporin treatment of uncomplicated respiratory infections with a presumed etiology has increased, despite the lack of clinical indication.[27,28] The appropriateness of cephalosporin use in such circumstances should be questioned and closely monitored in compliance with existing guidelines for treatment of respiratory tract infections.

We noted a shift from the quinolones that were predominantly used to treat urinary tract infections (pipemidic acid, norfloxacin) to those used systematically (ofloxacin, ciprofloxacin, levofloxacin). In addition, the use of quinolones in treatment of respiratory infections (third generation moxifloxacin) has increased over time, similar to the ESAC study findings on outpatient quinolone use in Europe.[29] Ciprofloxacin was the most prescribed quinolone with a continous increase in utilization (Table 2). Our rising quinolones utilization should be closely monitored in the view of seasonal variations, because other studies indicate a substantial increase in use of respiratory quinolones as well as an increase in use of so-called urinary tract quinolones, e.g. ciprofloxacin, in the winter months.[28] This inappropriate use of both older and respiratory quinolones will inevitably lead to emergence of resistant pneumococci, *Escherichia coli* and also of resistant Gram-negative bacteria.[29,30] Removal of subsidisation in Denmark of both tetracyclines and fluoroquinolones resulted in a rapid drop in utilization of these antibiotics.[3] Norfloxacine is now the only reimbursed quinolone. Tetracycline use with high seasonal variations declined significantly in the European countries. This may reflect the fact that prescription of antibiotics for respiratory tract infection is limited.[31] Doxycyclin was the third most prescribed antibiotic over the five year period of observation, but its use has diminished. Because of problems with resistance, doxycylin is no longer among the antibiotics recommended in the Netherlands for lower respiratory tract infections.[31,32]

Like in most European countries, we also noted that the newer antibiotics in almost all classes displaced older drugs, although narrow-spectrum and first-generation penicillins are still widely prescribed for treatment of community-acquired infections in certain northern European countries.[3] Pharma-

ceutical marketing can make doctors less sensitive to the costs and quality of prescribing drugs, and influence their choice of competing drugs, as observed in the Netherlands.[3] This could account for the growing use of newer antibiotics, [3] although most physicians eventually switch to newer antibiotics.[12]

Diagnostic labelling of respiratory tract infections as commom cold or bronchitis can affect antibiotic use as well, along with the propinsity of some physicians (high prescribers) to diagnose more bacterial infections than others (low prescribers).[33] Under the capitation payment scheme, our doctors have less incentive to prescribe antibiotics, and the quality of treatment is not directly related to the quantity of antibiotics prescribed. Instead, it may be improved by our doctors' ability to solicit patient compliance and reduce inappropriate antibiotic use. Educated individuals may refrain from using antibiotics because they are concerned about contributing to increased bacterial resistance.[12] A combination of educational and restrictive interventions seems to be more efficient than any single intervention for reduction of antibiotic utilization.[15]

Thus far, data on the extent of antibiotic resistance and utilization are limited in the Republic of Srpska, although several studies[2,3] indicate a correlation between antibiotic resistance and outpatient antibiotic use. However, a steady decline in utilization of some antimicrobial drug classes does not reflect concomitant decline of resistance in pathogens under selective pressure. Mathematical models, as well empirical data, suggest that after reduction in prescribing, resistance will take longer to decline than it took to rise.[34] For example, no decline in resistance against co-trimoxazole was observed in the United Kingdom even 10 years after it was no longer precribed.[35] Besides legislative regulating of prescribing and dispensing of anibiotics, our policy interventions to improve antibiotics use included standard treatment guidelines, reimbursment prescribing policy restricted to first-generation antibiotics and infection prevention (infection control and immunization). Unfortunately, comprehensive and systematic data on interventions designed to control outpatient antibiotic utilization are limited.

In conclusion, outpatient use of systemic antibiotics in the Republic of Srpska does not exceed that in Europe. The trends in time and the shift between generations in our antibiotic use need further examination, including monitoring of seasonal variation and antibiotic resistance impact on antibiotic use. Better and continuous surveillance of antibiotic use and resistance rates, optimization of antibiotic use with diagnostic tests, strict compliance to the guidelines, and education of professionals and public could all improve antibiotic therapy in our community and others.

Authorship statement

All authors contributed equally.

Financial disclosure

We declare that we have no conflicts of interest.

References

1. Minalu G, Aerts M, Coenen S, et al. Application of mixed-effects models to study the country-specific outpatient antibiotic use in Europe: a tutorial on longitudinal data analysis. J Antimicrob Chemother 2001;66:vi79-vi87.
2. Filippini M, González Ortiz L, Masiero G. Assessing the impact of antibiotic policies in Europe. Quaderno n. 12-02. Decanato della Facoltà di Scienze economiche. Lugano, 2011.
3. Goosens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance a cross-national database study. Lancet 2005;365:579-87.
4. European Centre for Disease Prevention and Control. Summary of the latest data on antibiotic consumption in the European Union, November 2012. Available at: http://www.ecdc.europa.eu/en/eaad/documents/esac-net-summary-antibiotic-consumption.pdf. Accessed January 30, 2013.
5. Wise R, Hart T, Cars O, et al. Antimicrobial resistance. BMJ 1998;317:609-10.
6. Grigoryan L, Haajer-Ruskamp F, Burgerdorf J, et al. Self-medication with antimicrobial drugs in Europe. Emerg Infect Dis 2006;12:452-59.
7. Marković-Peković V, Grubiša N. Self-medication with antibiotics in the Republic of Srpska community pharmacies: pharmacy staff behavior. Pharmacoepidemiol Drug Safety 2012;21:1130–33.
8. Gold HS, Moellering RC. Antimicrobial drug resistance. N Engl J Med 1996;335:1445-53.
9. McGowan JE.Economic impact of antimicrobial resistance. Emerg Infect Dis 2001;7:286–92.
10. Sabes-Figuera R, Segú J, Puig-Junoy J, et al. Influence of bacterial resistances on the efficiency of antibiotic treatments for community-acquired pneumonia. Eur J Health Econ 2008;9:23-32.
11. Elseviers M, Ferech M, Vander Stichele R, et al. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf 2007; 16:115-23.
12. Masiero G, Filippini M, Ferech M, et al. Socioeconomic determinants of outpatient antibiotic use in Europe. Int J Public Health 2010;55:469–78.
13. Filippini M, Masiero G, Moschetti K. Socioeconomics determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland. Health Policy 2006;78:77-92.
14. Molstad S, Stalsby Lundborg C, Karlsson A, et al. Antibiotic Prescription Rates Vary Markedly Between 13 European Countries. Scand J Infect Dis 2002; 34:366-71.
15. Čižman M, Srovin T, Pokorn M, et al. Analysis of the causes and consequences of decreased antibiotic consumption over last 5 years in Slovenia. J Antimicrob Chemotherapy 2005;55:758-63.
16. Ferech M, Coenen S, Dvorakova K, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient penicillin use in Europe. J Antimicrob Chemother 2006;58:408-12
17. Marković-Peković V, Stoisavljević-Šatara S. Outpatient utilization of antibiotics in the Republic of Srpska, in 2007 and 2008. Scr Med 2010; 41:22-28.
18. WHO Collaborating Centre for Drug Statistics Methodology. ATC Index with DDDs. WHO, Oslo. Available at: http://www.

whocc.no/atc_ddd_publications/guidelines/. Accessed January 30, 2013.
19. Monnet A, Molstad S, Cars O. Defined daily doses of antimicrobials reflect antimicrobial prescriptions in ambulatory care. J Antimicrob Chemother 2004; 53:1109-11.
20. Republic of Srpska Institute of Statistics. Statistical Yearbook of Republic of Srpska. Banja Luka, 2012.
21. Adriaenssens N, Coenen S, Muller A, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997-2009). J Antimicrob Chemother 2011;66: vi3-vi12.
22. Bergan T. Antibiotic usage in Nordic countries. Int J Antimicrob Agents 2001;18:279-82.
23. Versporten A, Coenen S, Adriaenssen N, et al. European Surveillance of Antimicrobial Consumption (ESAC):outpatient penicillin use in Europe (1997-2009). J Antimicrob Chemother 2011;66:vi13-vi23.
24. Centre for Clinical Practice at NICE (UK). Respiratory Tract Infections—Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care. NICE Clinical Guideline 69, July 2008. National Institute for Health and Clinical Excellence, London, UK. Available at: www.nice.org.uk/nicemedia/pdf/ CG69FullGuideline.pdf. Accessed February 8, 2013.
25. National Agency for Medicines and the Social Insurance Institution (Kela). Finnish statistics on medicines. Available at: http://www.fimea.fi/instancedata/prime_product_julkaisu/fimea/embeds/fimeawwwstructure/20681_Suomen_laaketilasto_2010_netti.PDF. Accessed January 25, 2013.
26. Statens Serum Institut, medstat.dk and date. Available at: http://www.medstat.dk/en. Accessed January 25, 2013.
27. Versporten A, Coenen S, Adriaenssen N, et al. European Surveillance of Antimicrobial Consumption (ESAC):outpatient cephalosporin use in Europe (1997-2009). J Antimicrob Chemother 2011;66:vi25-vi35.
28. Woodhead M. Prescribing and guidelines: both must improve to combat antimicrobial resistance. Eur Respir J 2011;38:9-11.
29. Adraenssen N, Coenen S, Versporten A, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient quinolone use in Europe (1997-2009) J Antimicrob Chemother 2011;66:vi47-vi56.
30. Čižman M. The use and resistance to antibiotics in the community. Int J Antimicrob Agents 2003; 21:297-307.
31. Coenen S, Adriaenssens N, Versporten A, at al. Antimicrobial Consumption (ESAC): outpatient use of tetracyclines, sulphonamides and trimethoprim, and other antibacterials in Europe (1997-2009) J Antimicrob Chemother 2011;66:vi57-vi70.
32. Verheij T, Hermans J, Mulder J. Effects of doxycycline in patients with acute cough and purulent sputum:a double blind placebo controlled trial. Br J Gen Pract 1994;44:400-4.
33. Hutchinson J, Jelinski S, Hefferton D, et al. Role of diagnostic labeling in antibiotic prescription. Can Fam Physician 2001;47:1217-24.
34. Austin D, Kristinsson K, Anderson R. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Poc Natl Acad Sci USA 1999; 96:1152-6.
35. Enne V, Livermore D, Stephens P, et al. Persistence of sulphonamide resistance in *Echerichia coli* in the UK despite national prescribing restriction. Lancet 2001;357:1325-8.

Vanbolnička upotreba antibiotika za sistemsku primjenu u Republici Srpskoj

APSTRAKT

Uvod. Još uvijek nema dovoljno objavljenih podataka o upotrebi antibiotika u Republici Srpskoj. Cilj ove studije je analizirati vanbolničku upotrebu antibiotika od 2007. do 2011. godine, i podatke uporediti sa podacima drugih Evropskih zemalja.

Materijal i metode. Da bi se analizirala vanbolnička upotreba antibiotika za sistemsku primjenu provedena je retrospektivna studija upotrebe lijekova, uz primjenu metodologije anatomsko-hemijsko-terapijske klasifikacije lijekova i definisane dnevne doze. Rezultati su izraženi u definisanim dnevnim dozama (DDD) na 1000 stanovnika na dan. Podaci su preuzeti iz godišnjih izvještaja Agencije za lijekove i medicinska sredstva Republike Srpske i Instituta za javno zdravstvo.

Rezultati. Vanbolnička upotreba antibiotika za sistemsku primjenu kretala se između 21,51 DDD u godini sa najvećom upotrebom (2010.) i 17,01 DDD u godini sa najnižom upotrebom (2011.). Penicilini su bili najčešće propisivana grupa antibiotika, a amoksicilin najpropisivaniji antibiotik. Cefaleksin je bio najčešće propisivan cefalosporinski antibiotik. Primijećen je porast upotrebe cefalosporina druge gerenacije cefuroksima, čija je upotreba 2011. godine činila trećinu upotrebe cefaleksina. Upotreba druge generacije hinolonskih antibiotika, uglavnom ciprofloksacina, činila je oko 70% ukupne upotrebe hinolonskih antibiotika, uz porast treće generacije hinolona. Eritromicin je bio najčešće propisivan makrolidni antibiotik, a slijedi dugodjelujući makrolidni antibiotik azitromicin.

Zaključak. Vanbolnička upotreba antibiotika za sistemski primjenu u Republici Srpskoj nije iznad evropskog prosjeka, i kreće se oko 19 DDD. Slično drugim evropskim zemljama, i kod nas je primijećen prelazak na propisivanje novijih generacija antibiotika. Potrebno je provesti daljnja istraživanja upotrebe antibiotika, uključujući i uticaj sezonskih varijacija na upotrebu.

KLJUČNE REČI

Antibiotici, upotreba lijekova, vanbolnička zdravstvena zaštita, farmakoepidemiologija.

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ORIGINAL ARTICLE

The Influence of Gender and Laterality of Lesion on Severity of Post-Stroke Depressive Symptoms

Sanja Drača

College of Applied Sciences
Kruševac 37000, Serbia

Correspondence
Sanja Drača, MD, PhD
College of Applied Sciences
Ćirila i Metodija 22-24
Kruševac 37000, Serbia
Phone: + 38137423050
Fax: + 38137420761
E-mail: sanjadraca9@gmail.com

ABSTRACT

Introduction. This prospective study evaluates the effects of gender and stroke lateralization-related differences on the severity of depressive symptoms.

Materials and Methods. A total of eighty right-handed patients (20-80 years of age) were enrolled prospectively. These individuals were in the subacute phase of their first, single unilateral stroke. Thirty-five (44%) were women. The majority of patients (74%) had cerebral infarcts, and 26% had an intracerebral hemorrhage. The Beck Depression Inventory (BDI) edition 2, was used to assess the severity of depressive symptoms. (A cutoff point of 14 or higher was applied to distinguish patients with depressive symptoms).

Results. At discharge from rehabilitation, the BDI-II identified depressive symptomatology in 33% of patients (n=26 patients). Although the frequency of depressive symptoms was similar in both sexes, we identified significant differences in the frequencies of post-stroke depressive symptoms between men and women with different localization of stroke. Females with poststroke depressive symptomatology were more likely to have a cortical lesion, whereas males with poststroke depressive symptomatology were more likely to have a subcortical lesion. We also noted that women had significantly more severe depressive symptoms (higher mean BDI-II scores) than men. In addition, the severity of depressive symptoms was related to the laterality of lesion in men but not in women. Men with left-sided stroke had significantly more severe depressive symptoms than men with right-sided stroke.

Conclusion. Our paper emphasizes the association of gender and laterality of lesion with the severity of post-stroke depressive symptoms.

KEY WORDS

Gender, stroke, lateralization, depressive symptoms.

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Common behavioral and cognitive sequalae of stroke include depression, psychosis, anxiety and personality changes among others.[1,2] The prevalence of post-stroke depression (PSD) is reported to range from less than 30% to more than 50%, depending on methodological differences between studies and especially on the criteria for depression and the period over which depression is assessed.[2,3]Neither the causes nor the mechanisms of PSD are well understood. The higher prevalence of mood symptoms in stroke survivors, as compared with orthopedic patients with the same degree of functional disability, argues against PSD as a purely psychological reaction.[4] PSD likely has a multifactorial etiology with both reactive and organic components. The evidence in humans suggests that injury of specific brain areas with hemispheric and anterior-posterior asymmetries increases the risk of developing PSD.

Robinson et al in a series of articles emphasized that left-sided stroke may be associated with a higher incidence of depression,[5,6] although some investigators were unable to replicate these results.[3] It has been suggested that the strength and direction of experienced emotions should be evaluated within the context of asymmetrical activation of left-frontal (dominance) versus right-frontal (submis-

sion) brain regions.[7] More recently, changes of noradrenergic, serotonergic, and dopaminergic pathways, and neurotransmitter receptor sensitivity have been implicated in the pathogenesis of PSD. The question of much higher lifetime prevalence of major depressive disorders in women compared to men, including stroke survivors, remains unanswered.[8,9] However, numerous gender-related differences in neuroanatomy and neurochemistry are documented. It appears that males and females recruit different brain regions during emotion recognition of happy or sad facial expression.[10] A wealth of preclinical and clinical evidence indicates gender-related differences in serotonin (5-hydroxytryptamine, 5-HT) neurotransmission.[11] Serotonin has been implicated in the pathology of mood disorders, sleep and eating disorders and schizophrenia.

It is important to emphasize that patients with improved depression perceived their recovery as significantly greater than those with continued depression; they also felt that their physical condition and social participation had improved in contrast to those with less improvement in depression.[12]

This prospective study was designed to evaluate the severity of depressive symptoms related to gender- and stroke lateralization in patients after their first, single unilateral stroke.

Materials and Methods

All patients in the subacute phase of stroke admitted to the rehabilitation clinic "Dr M. Zotović" in Belgrade, during a 3-year period were registered prospectively and considered for inclusion for this study. The mean time period from the onset of illness to admission into the study was 91.7 days. During the acute phase of stroke the patients were hospitalized at neurology departments in several hospitals, where the diagnosis of stroke was based on history, clinical examination and neuroradiological findings obtained by head computed tomography (CT) or magnetic resonance imaging (MRI).

On admission to rehabilitation, all patients were assessed by clinical and neurological examinations and neuropsychological and language testing. The severity of the initial stroke was measured by the National Institutes of Health Stroke Scale (NIHSS) score, which is a widely used and validated tool for assessment of stroke severity.[13] According to CT and/or MRI findings, the patients were classified based on localization of the cerebral lesion in the right hemisphere (RH) or left hemisphere (LH) as well as in the cortex or subcortex.

Inclusion criteria were: the first-ever single unilateral stroke, both genders, age 20-80 years, CT or MRI examination performed in the acute hospital phase of stroke and right-handedness (defined by the Clinical test of hand dominance, Kimura & Vanderwolf, 1970). Exclusion criteria were: history of previous stroke, bilateral or multiple cerebral lesions caused by stroke, history of previous psychiatric illness, severe post-stroke cognitive impairment, severe post-stroke aphasia and presence of chronic disabling conditions. None of the selected patients were treated with antidepressant medication or any drug with depression as a known side effect.

The rehabilitation plan was designed by the same physiatrist for all patients; it included physical therapy, occupational therapy, and if necessary, speech therapy. The rehabilitation program was performed 5 days per week over 6-8 consecutive weeks. All patients included in this study completed the rehabilitation program. After receiving a detailed study description, participants provided informed consent to a research protocol, which was carried out in accordance the principles of the Declaration of Helsinki (1964).

At the time of discharge, on average 5.5 months after stroke onset (range 3.5-6 months), we evaluated the severity of PSD. The patients completed the 21-item Beck Depression Inventory, edition 2 (BDI-II), which is a screening instrument designed to assess the severity of depression, not whether a patient meets diagnostic criteria for that disorder.[14] The inventory contains 21 items and identifies symptoms and attitudes associated with depression. The respondent must recall, based on the previous two weeks, the relevance of each statement relating to the following: sadness, pessimism, sense of failure, loss of pleasure, guilt, expectation of punishment, dislike of self, self accusation, suicidal ideation, episodes of crying, irritability, social withdrawal, indecisiveness, worthlessness, loss of energy, insomnia, irritability, loss of appetite, preoccupation, fatigue, and loss of interest in sex. A BDI-II cutoff point of 14 or higher was applied to distinguish the patients with a depressive symptomatology in the clinical range from those with less severe symptomatology.

Statistical analysis. Characteristics of the participants are described by mean and standard deviation (SD) for continuous variables and by frequency and percentage for categorical variables. A difference in mean values of BDI-II or NIHSS scores between two groups of patients was determined by Student t-test. The chi square test was used to assess differences in categorical variables between men and women. Probability values <0.05 were considered significant.

Results

A total of eighty right-handed patients (mean age 55.4 years, SD = 10.6 years, range 20-80 years) in the subacute phase of their first-ever single unilateral stroke were enrolled prospectively. Thirty-five (44%) were female, and 45 (56%) were male. There was no significant difference in mean ages between men and women (55.1 and 55.6, respectively).

Fifty-seven % of females (20 of 35), and 45% of males (20 of 45) had a stroke in the LH, whereas 43 % of females (15 of 35) and 55% of males (25 of 45) had a stroke in the RH. Further, 57 % of females (20 of 35), and 40 % (18 of 45) of males had a stroke localized cortically, whereas 43 % of females (15 of 35) and 60 % of males (27 of 45) had a subcortical stroke. Prior to the initiation of rehabilitation the mean NIHSS score was similar for both men (6.51) and women (6.57) (Table 1).

Table 1. Frequencies of post-stroke depressive symptomatology in men and women with different localization of stroke (Chi square test = 14.197; DF = 3; p<0.01)

Stroke localization	Frequency (n)
Women (n = 12 with depressive symptoms)	
RH cortically	33 % (4 of 12)
LH cortically	50 % (6 of 12)
RH subcortically	0 % (0 of 12)
LH subcortically	17 % (2 of 12)
Men (n = 14 with depressive symptoms)	
RH cortically	14 % (2 of 14)
LH cortically	0 % (0 of 14)
RH subcortically	29 % (4 of 12)
LH subcortically	57 % (8 of 14)

Abbreviations: RH = right hemisphere, LH = left hemisphere

Frequency and severity of post-stroke depressive symptomatology

At discharge from rehabilitation, the BDI-II identified depressive symptomatology in 33% of patients (26 of 80) where the cutoff point of 14 or higher was applied. The frequency of depressive symptoms in the clinical range was 32% in males (14 of 45) and 34% in females (12 of 35). There was no significant difference between these frequencies (Chi square test = 0.09; DF = 1; p>0.05). However, we identified a significant (p<0.01) difference in the frequencies of post-stroke depressive symptoms between men and women with different localizations of stroke (Chi square test = 14.197; DF = 3; p<0.01). Females with poststroke depressive symptomatology were more likely to have a cortical lesion (83%, 10 of 12 patients), whereas males with poststroke depressive symptomatology were more likely to have a subcortical lesion (86%, 12 of 14 patients, Table 1).

We also found that women had significantly (p<0.01) more severe depressive symptoms (higher mean BDI-II score) than men. The severity of depression was dependent on stroke lateralization in males, but not in females. Men with left-sided stroke had significantly (p<0.01) more severe depressive symptoms (higher mean BDI-II score) than men with right-sided stroke (Table 2).

Discussion

The frequency of depressive symptoms (33%) in our study is comparable to the prevalence of PSD reported in previous clinical trials. The prevalence of PSD ranges from less than 30% to more than 50%, depending on the methodological differences between studies, specifically the criteria for depression and the period over which depression is assessed.[2,3]

Bearing in mind that previous clinical trials indicate that recognized risk factors for post-stroke depression include stroke severity and disability, it is important to note that prior to initiation of rehabilitation we noted no gender-related difference in the severity of clinical stroke. However, we found that women with a first-ever single unilateral stroke had significantly more severe depressive symptoms than men. Furthermore, the severity of symptoms was related to the laterality of lesion in men, but not in women. Men with left-sided stroke had significantly more severe depressive symptoms than men with right-sided stroke. Our results concur with previous studies that demonstrated a greater prevalence of post-stroke depressive symptoms in women than in men. However, all of these results remain inconclusive because the question of much higher lifetime prevalence of major depressive disorders in women remains unanswered.[9]

Gender-related differences in neuroanatomy and neurochemistry have drawn increasing interest over the past

Table 2. Differences in mean values of BDI-II scores between men and women, as well as between men or women with right-sided or left-sided stroke

	Men/Women (n = 45) (n = 35)	Men RH/Men LH (n = 25) (n = 20)	Women RH/Women LH (n =15) (n=20)
BDI-II Mean (SD)	10.14 (7.30)/13.25 (8.35)	8.96 (6.92)/11.60 (7.51)	12.47 (7.97)/13.85 (8.74)
T	4.568 (DF =78)	3.198 (DF =43)	1.211 (DF =33)
P	<0.01	<0.01	>0.05

Abbreviations: BDI = Beck Depression Inventory, SD = standard deviation, RH = right hemisphere, LH = left hemisphere.

decades, including differences in the size of brain nuclei, regional concentrations of neuroregulators, pharmacological response and behavior.[9,12] Men synthesize 5-HT significantly faster than women,[15] whereas 5-HT transporters are selectively decreased in an age-specific manner in depressed women, but not in depressed men.[10] Also, gender-specific differences are apparent in brain regions involved in regulating negative or positive emotions.[11,16,17] Numerous clinical measurements on functional cerebral asymmetries indicate that women are less lateralized than men for a variety of cerebral functions. The facial recognition of emotion is distributed more bilaterally in females compared to males, whereas studies of transient mood induction triggered by viewing emotional pictures registered more neural activities in the bilateral superior temporal gyri and cerebellar vermis in females who viewed negative emotional pictures than in male viewers.[18-20] Furthermore, reports on gender-specific differences in hemispheric recruitment suggest that men are right-hemisphere dominant, while the female pattern indicates dominance of the left hemisphere.[21] Importantly, functional cerebral asymmetries likely fluctuate across the menstrual cycle as a result of estrogen and/or progesterone-related modulation of inter-hemispheric inhibition.[22]

Evidence suggests that the injury of specific brain areas in humans increases the risk of developing PSD. In particular, the occurrence of PSD has been linked to injuries of the left anterior frontal lobe and left caudate nucleus, as well as bilateral injuries of the anterior frontal and temporal lobes and caudate nuclei.[6,23] Astrom et al. found that a left-sided lesion was the most important predictor of immediate depression; the occurrence of major depression in left-sided lesions was 10 times greater than in lesions in the right hemisphere.[24] Some other authors have been unable to replicate this association of lesion location and PSD.[3]

A wealth of preclinical and clinical evidence supports the concept of functional cerebral asymmetries for neurotransmitter systems, including neurotransmitter levels, reuptake transporters and receptors, and the effects of drugs that act on these neurotransmitter systems. Two decades ago Mayberg et al. reported right-left asymmetry in functioning of serotonin in healthy normal subjects and stroke patients.[25] Later Fitzgerald suggested that 5-HT preferentially activates the right hemisphere through some unknown mechanism.[26] Postmortem binding studies done with brain tissue from mentally normal humans and the tricyclic antidepressant imipramine (which binds with high affinity to the 5-HT reuptake transporter) indicated higher binding values in the orbitofrontal cortex (connected by the efferent projections with the serotonergic raphe nuclei) of the right hemisphere than in the left hemisphere.[27,28]

If men are more lateralized than women for a variety of cerebral functions,[18-20] if the male pattern of dominance is characterized by the right hemisphere,[21] and if there is serotonergic predominance in the right hemisphere, [26] this might explain why we found more severe depressive symptoms in men with left-sided lesions.

We recognize that our study has limitations. The sample size is small, and the stroke patients participating in the study cannot be considered a random sample. We assessed the severity of depressive symptoms, but not the presence of a diagnosis of depression. For all these reasons, the results of this study cannot be generalized to the entire population of unselected stroke survivors. Despite these shortcomings, our paper emphasizes the association of gender and laterality of lesion with the severity of post-stroke depressive symptoms. The nature of this complex association requires further investigation with a larger number of patients and tools for examining neurotransmitter systems.

Financial disclosure
I declare that I have no conflicts of interest.

References

1. Starkstein SE, Robinson RG. Neuropsychiatric aspects of cerebral vascular disorders. In: Yudofsky SC, Hales RE, editors. The American Psychiatric Textbook of Neuropsychiatry. Washington DC, APA Press, 1992.
2. Kneebone II, Lincoln NB. Psychological Problems after Stroke and Their Management: State of Knowledge. Neurosci Med 2012;3:83-9.
3. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: A systematic review of observational studies. Stroke 2005;36:1330–40.
4. Folstein MF, Maiberger R, McHugh PR. Mood disorder as a specific complication of stroke. J Neurol Neurosurg Psychiatry 1977;40:1018 –20.
5. Morris PL, Robinson RG, Raphael B, Hopwood MJ. Lesion location and post-stroke depression. J Neuropsychiatry Clin Neurosci 1996;8:399–403.
6. Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long/term follow up. Biol Psychiatry 1999;45:187-92.
7. Demaree HA, Everhart DE, Youngstrom EA, Harrison DW. Brain lateralization of emotional processing: Historical roots and a future incorporating "Dominance". Behav Cogn Neurosci Rev 2005;4:3-20.
8. Paradiso S, Robinson RG. Gender differences in post-stroke depression. J Neuropsych Clin Neurosci 1998;10:41-7.
9. Angst J, Gamma A, Gatspar M, Lepine JP, Mendlewicz J, Tylee A. Gender differences in depression: Epidemiological findings from the European DEPRES I and II studies. Eur Arch Psychiatry Clin Neurosci 2002;252:201-9.
10. Lee TMC, Liu HL, Hoosain R, Liao WT, Wu CT, Yuen KSL. Gender differences in neural correlates of recognition of happy and sad faces in humans assessed by functional magnetic imaging. Neurosci Lett 2002;333:13-16.
11. Staley J, Sanacora G, Tamagnan G et al. Sex differences in diencephalon serotonin transporter availability in major depression. Biol Psychiatry 2005;59:40–7.

12. Saxena SK, Ng TP, Koh G, Yong D, Fong NP. Is improvement in impaired cognition and depressive symptoms in post-stroke patients associated with recovery in activities of daily living? Acta Neurol Scand 2007;115:339–46.
13. Adams HP Jr, del Zoppo G, Alberts MJ et al. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/ American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38:1655-711.
14. Aben I, Verhey F, Lousberg R, Lodder J, Honig A. Validity of Beck Depression Inventory, Hospital Anxiety and Depression Scale, SCL-90, and Hamilton Depression Rating Scale as screeening instruments for depression in stroke patients. Psychosomatics 2002;43:386-93.
15. Nishizawa S, Benkelfat C, Young S et al. Differences between males and females in rates of serotonin synthesis in human brain. Proc Natl Acad Sci USA 1997;94:5308–13.
16. Hofer A, Siedentopf CM, Ischebeck A, Rottenbacher MA, Verius M. Gender differences in regional cerebral activity during the perception of emotion: A fMRI study. Neuroimage 2006;32:854-62.
17. Mak AKY, Hu Z, Zhang JXX, Xiao Z, Lee TMC. Sex-related differences in neural activity during emotion regulation. Neuropsychologia 2009;47:2900-8.
18. Crucian GP, Berenbaum SA. Sex differences in right hemisphere tasks. Brain Cogn 1998;36:377–89.
19. Drača S. Gender-specific functional cerebral asymmetries and unilateral cerebral lesion sequalae. Rev Neurosci 2010;21:421-5.
20. Borod J. Interhemispheric and intrahemispheric control of emotions: a focus on unilateral brain damage. J Consult Clin Psychol 1992;60:339-48.
21. Drača S. Differences in cerebrogenic cardiac disturbance in men and women. Lancet Neurol 2012;11:842.
22. Hausmann M. Functional cerebral asymmetries during the menstrual cycle: a crossectional and longitudinal analysis. Neuropsychologia 2002;40:808-16.
23. Tuppler LA, Ranga K, Krishnan R et al. Anatomic location and laterality of MRI signal hyper-intensities in late-life depression. J Psychosom Res 2002;53:665–76.
24. Astrom M, Adolfsonn R, Asplund K. Major depression in stroke patients: a 3-year longitudinal study. Stroke 1993;24:976–82.
25. Mayberg HS, Robinson RG, Wong DF, et al. PET imaging of cortical S2-serotonin receptors after stroke; lateralized changes and relationship to depression. Am J Psychiatry 1988;145:937-43.
26. Fitzgerald PJ. Whose side are you on: Does serotonin preferentially activate the right hemisphere and norepinephrine the left? Med Hypotheses 2012:79;250-4.
27. Demeter E, Tekes K, Majorossy K, et al. The asymmetry of 3H-imipramine binding may predict psychiatric illness. Life Sci 1989;44:1403–10.
28. Arato M, Frecska E, Tekes K, MacCrimmon DJ. Serotonergic interhemispheric asymmetry: gender difference in the orbital cortex. Acta Psychiatr Scand 1991;84:110–11.

Uticaj pola i lateralizacije lezije na težinu postapoplektične depresivnosti

APSTRAKT

Uvod. Cilj ove prospektivne studije bio je da se utvrdi postojanje razlika u težini postapoplektične depresivnosti u zavisnosti od pola i lateralizacije lezije.

Materijal i metode. Uključeno je ukupno 80 desnorukih bolesnika u subakutnoj fazi prvog unilateralnog moždanog udara, starosti 20-80 godina. Od ukupnog broja bolesnika 35 (44%) su bile žene. Prema kategoriji moždanog udara, 59 (74%) bolesnika je imalo cerebralnu ishemiju, a 21 (26%) intracerebralnu hemoragiju. Kao instrument istraživanja je korišćena Bekova skala za procenu depresivnosti-II (upotrebljen je granični skor 14).

Rezultati. Po završetku rehabilitacije, registrovana je postapoplektična depresivnost u 33% (n=26) bolesnika. Iako je učestalost postapoplektične depresivnosti bila približno jednaka kod oba pola, registrovana je značajna razlika u učestalosti postapoplektične depresivnosti između polova sa različitom lokalizacijom moždanog udara. Žene sa utvrđenom depresivnom simptomatologijom su značajno češće imale leziju korteksa, dok su muškarci sa utvrđenom depresivnom simptomatologijom značajno češće imali leziju subkorteksa. Pokazano je da žene ispoljavaju značajno težu simptomatologiju postapoplektične depresije (više srednje vrednosti BDI-II skora) u odnosu na muškarce. Takođe, registrovana je statistički značajna razlika u težini depresivne simptomatologije u zavisnosti od lateralizacije lezije kod muškaraca, ali ne i kod žena.

Zaključak. Rezultati ove studije ukazuju na značaj pola i lateralizacije lezije na težinu postapoplektične depresivne simptomatologije.

KLJUČNE REČI

Pol, moždani udar, lateralizacia, depresivni simptomi.

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ORIGINAL ARTICLE

Abbreviated UVA-Riboflavin Corneal Collagen Cross-linking for Keratoconus and Post-LASIK Ectasia

Robert L. Epstein
Greg L. Epstein

College of Applied Sciences
Mercy Center for Corrective Eye Surgery
McHenry, Illinois

Correspondence
Robert L. Epstein, MD, MSEE
Mercy Center for Corrective Eye Surgery
McHenry, IL USA
Email: rlepstein@aol.com

ABSTRACT

Introduction. To determine the effect of corneal collagen cross-linking treatment on keratoconus and post-LASIK ectasia particularly after an abbreviated exposure to ultraviolet light exposure.

Materials and methods. Fifty-one eyes of 34 patients were treated with epithelium-off UVA-riboflavin corneal collagen cross-linking for either 20 minutes or 30 minutes as part of a US.FDA clinical study. The study involved eyes with keratoconus but with no prior operation (virginal), patients who had undergone prior intracorneal ring segments, those with keratoconus regression after keratoplasty, and those with post-LASIK ectasia. We report follow up results from three months to one year.

Results. In the virginal keratoconus group all 83% of eyes having 20-minute UVA exposure and 75% of those having 30-minute of UVA exposure experienced corneal flattening or stabilization at 6 months post-operatively with visual improvement in both groups. The average patient age in the virginal keratoconus group was 34.5 years. Seventy five percent of virginal keratoconus eyes of patients under age 40 but only 33% of eyes of patients over age 40 experienced statistically significant corneal flattening at six months postoperatively. Average vision improved at six months post-operatively over pre-operative levels by -0.0744 logMAR units in the 20 minute group, and by -0.0869 logMAR units in the 30 minute group. Post-LASIK ectasia patients, with an average age of 58.2 years, had slight overall curvature flattening of -0.75D but without visual improvement one year post-operatively. No one experienced peri-operative complications. Topographic subtraction mapping revealed variations in the power of the cross-linking effect on different portions of the cornea

Conclusion. Cross-linking appears safe. It is effective in most young patients causing corneal flattening and can stabilize eyes with post LASIK ectasia but acts more slowly in older patients. The cross-linking effect may be more pronounced in individuals with darker pigmentation. Cross-linking can produce occasional very significant corneal flattening. The cross-linking effect increases with time.

KEY WORDS

Cross-linking, keratoconus, riboflavin, post-LASIK ectasia, collagen cross-linking

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Keratoconus is an important cause of visual loss that can severely affect relatively young and otherwise apparently healthy people. Also there is association of keratoconus with disease. Keratoconus is associated with eczema, allergy and asthma [1], as well as with Marfan syndrome and with Down syndrome [2]. There is a high incidence of sleep apnea among keratoconus patients [3,] and keratoconus patients may have reduced life expectancy [4].

Early visual decline may resemble the optical changes of youth. But what is not normal is the need for increasing astigmatic correction that is typically seen in developing

keratoconus. With disease progression eyeglasses cannot correct vision to normal. Visual loss from keratoconus is often misdiagnosed at first as being from amblyopia unless there is a search for and comparison with old records from previous eye doctors. Soft lenses and then rigid contact lenses become necessary for adequate vision, but when these lenses become increasingly uncomfortable and more poorly fitting, surgical treatment is necessary to improve vision. Vigorous eye rubbing makes the disease worse and patients should be discouraged from this practice.[5,6]

The mainstay of surgical treatment for keratoconus has included corneal transplantation with its long healing period, risk of rejection, infection, and corneal rupture. Commonly transplantation requires the patient to wear rigid contact lenses after surgery in order to achieve optimum vision. Surface excimer laser treatment of the cornea after healing may be indicated to help vision in some cases. Corneal grafting, either full thickness or deep anterior lamellar keratoplasty remains necessary for some cases of advanced keratoconus, yet even that may not stop visual decline because keratoconus persists in the host cornea.

More recently, the implantation into the corneal wall of two, or possibly more effectively just one[7], polymethy methacrylate ring segment has helped to regularize the shape of the keratoconus cornea. However, this bracing effect does not stop the basic disease process which usually continues.

A condition called post-LASIK ectasia can occur as a result of the normal sculpting of the cornea in laser refractive surgery, including either LASIK or the surface laser vision correction known as PRK. It closely mimics the visual distortion of keratoconus. Some of the victims of post-LASIK ectasia may have had an unrecognized early stage of keratoconus, or *forme fruste* keratoconus, but others show no signs of the disease whatsoever, even when tested by any method in current technology. Detection of risk factors for post-LASIK ectasia is a subject of considerable interest and research. [8-14] An increased number of patients with *forme fruste* keratoconus tend to seek laser vision correction; the incidence has been documented to be in some cases as high as 9%. [15] Fortunately, some years ago Spoerl, Huhle, and Seiler [16] published a procedure called corneal collagen cross-linking with riboflavin that provided a partial solution to the problem of ectatic and keratoconic corneas. Studies from their institute and many others have advanced the field with over 400 papers having been published since that time.

Although the complete mechanism of keratoconus is not known, it is due in part to inadequate cross-linkages between collagen fibrils in the cornea and further degradation by metalloproteinases. [17,18] Corneal collagen cross-linking with riboflavin is an oxidatative process that riboflavin promotes in the presence of ultraviolet light. Cross-linking causes immediate corneal stiffening even in cadaver tissue. Along with that stiffening cross-linking causes actual keratocyte destruction, swelling and corneal stromal remodeling in living corneas. [19,20] Riboflavin presently is critical to the cross-linking process and riboflavin penetrates poorly [21] through an intact corneal epithelium, however much work is occurring to increase the epithelial permeability including recently the addition on an experimental basis of vitamin E TPGS to the riboflavin solution[22].

Collagen cross-linking is a successful adjunct to the use of antibiotics in certain difficult corneal infections [22,] and there is evidence that cross-linking may actually reduce the degree of edema and improve vision in some patients with persistent corneal edema occurring after cataract surgery and corneal edema from Fuchs' dystrophy [23]. Corneal collagen cross-linking is not yet approved by the United States Food and Drug Administration (US FDA) although it is freely available in certain eye centers worldwide

Materials and Methods

Fifty-one eyes of 34 patients underwent UVA-riboflavin, corneal collagen cross-linking, with epithelial removal. This was the first part of a three year clinical study on the safety and effectiveness of cross-linking as well as a comparison of the relative effects of 30 minutes versus 20 minutes of ultraviolet exposure. Cross-linking was performed for eyes with advancing keratoconus, with post-LASIK ectasia, and with advancing keratoconus recurring years after corneal transplantation. This report details the results of the cross-linking in forty-five eyes where patients were re-evaluated with three months to one year of follow up.

All patients received complete eye exams at each visit including endothelial cell photography and also five Pentacam Scheimpflug photographs of each eye.

Individuals who would most likely benefit from cross-linking and also from intracorneal ring segments (ICRS) were given a choice of two protocols: either having ICRS first and cross-linking 90 days later or having cross-linking first, then ICRS one year later.

Because the measure, maximal anterior corneal curvature, Kmax, is the most sensitive indicator of corneal curvature change from cross-linking, [24] those values were tabulated as part of the current clinical study. We have shown [25] that based on a comparison of the average of five Kmax values taken at each visit, the 95% confidence level of true Kmax change is a measured difference of at least 0.678 D using the Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany). Thus, one reasonable criterion for judging the efficacy of cross-linking is a change of 0.678D or more Kmax based on five readings. That criterion is used here.

All eyes in the study had the cross-linking procedure following the removal of corneal epithelium. Then an initial

14 minute corneal soaking was done by dripping 0.1% riboflavin upon the cornea every two minutes. This step was followed by the application by random assignment of either 20 minutes or 30 minutes of ultraviolet light at 370 nm using the UV-X device (Peschke Meditrade, Huenenberg, Switzerland). Either Mediocross brand (Streuli Pharma distributed by Peschke Meditrade) isotonic riboflavin 0.1% in 20% dextran or the hypotonic 0.10% riboflavin in 0.9% saline was used based on the minimal corneal pachymetry readings. All patients signed detailed consent forms, and the clinical study was performed in a manner approved by both the U.S. Food and Drug Administration and by the Institutional Review Board of the Mercy Health System, the parent company of this surgical practice. SPSS 16.0 (IBM Armonk, New York , USA) and Excel 2007 (Microsoft Corp. Redmond, WA, USA) were used for the statistical analyses.

Cross-linking was done under sterile conditions. Pachymetry of each eye averaged at least 400 microns throughout the treatment. Any eye undergoing cross-linking that developed stromal corneal pachymetry less than 410 microns was treated with hypotonic riboflavin, and the thicker corneas were cross-linked with isotonic riboflavin. Ultrasonic pachymetry was measured at three minute intervals. Under rare circumstances when pachymetry dipped below 400 microns during cross-linking a single drop of sterile water was applied to the cornea. Within seconds this treatment increased the corneal thickness by 20 microns or more. Epithelium was removable gently with an Amoils brush but for post-surgical eyes just ten seconds of 70% ethanol and gentle rubbing with a WeckCell sponge was found to be sufficient. All eyes with post-LASIK ectasia had epithelium removed using alcohol rather than the Amoils brush. In general the epithelium in eyes with keratoconus was found to be less firmly attached than in normal eyes.

Eyes in our study included those with virginal keratoconus and no prior surgery, those with prior refractive surgery, those with prior intracorneal ring treatment, and those with prior corneal transplantation for keratoconus. Included in the study were a total of 41 eyes with virginal keratoconus, that is, keratoconus as distinguished from post-LASIK ectasia in eyes that had not had intracorneal ring placement or corneal transplantation. Of these 41 eyes, 36 were at least one month post cross-linking. The overall patient age in the study was 38.9 +/-13.7 years with the post-LASIK ectasia patients being considerably older at 58.2 +/-4.6 years and the keratoconus patients being 34.5 +/-11.5 years.

Results

None of our patients had any operative or peri-operative complications. Corneal edema was common during the first week. Except in the younger patients, correctable vision typically was better pre-operatively than one month post-operatively

There was no tendency towards endothelial cell loss. In the combined group, the pre-operative average cell count was 2306 +/- 590. Cross-linking resulted in essentially no change in endothelial cell count. Cell count changes from the pre-operative level were -2.9%+/-13.2%, +1%+/-28.3%, -5.2% +/-14.1%, and -0.2% +/-17.4% at one month, three months, six months and one year postoperatively respectively.

There were no patient complaints of dry eye occurring after cross-linking that had not also been documented preoperatively.

Tables 1 through 4 describe the behavior of the corneal curvature, as measured by maximal anterior equivalent keratometry, Kmax. Table 1 documents the number of statistically significant increases and decreases of Kmax at six months postoperatively. Based on the modest sample size, results from both the twenty and thirty minute UV-A riboflavin cross-linking treatments appeared to be equivalent six months postoperatively. In Table 2 shows that there was a general tendency for some reduction in the curvature of the cornea in most patients by six months postoperatively and this effect was first noticeable at three months postoperatively.

Table 1. Behavior of Kmax at 6 months postoperative after collagen cross-linking in virginal keratoconus eyes (no LASIK, corneal transplant, or intracorneal rings)

Group----->	20 minute	30 minute
Kmax		
Decrease(better)	9	6
Increase(worse)	2	3
Same	0	3

Note: "Same" is defined as having the five easurement post-operative Kmax average within 0.678D or pre-operative average

Table 2. Behavior of Kmax after Collagen Cross-linking by Postoperative Time All eyes including virginal keratoconus, post-LASIK ectasia, post Intrstromal rings, and post corneal transplant

	1 month	3 months	6months	1 year
Kmax				
Decrease(better)	13(28.3%)	15(41.7%)	18(52.9%)	7(53.8%)
Increase(worse)	19(41.3%)	12(33.3%)	11(32.4%)	4(28.6%)
Same	14(32.7%)	9(25%)	5(14.7%)	3(21.4%)

Note: Same=Five measurement Kmax average is within 0.678D or pre-operative average

Despite the small sample size, Table 3 shows that cross-linking reduces or stabilizes the maximal corneal curvature of post-LASIK ectasia eyes similarly to what is seen in keratoconic eyes. However, it had a slightly weaker effect

on the ectasia eyes that visible at all until six months. Table 4 lists results from the combined group of virginal keratoconic eyes and shows a continuing and increasing cross-linking effect on the maximal corneal curvature extending beyond six months.

Five eyes were cross-linked after having had intracorneal ring segments (ICRS) at least three months before. Four had ICRS for keratoconus and one had ICRS for post-LASIK ectasia. The Kmax values of those eyes decreased an average of -2.12 D (range -0.94 to -2.82 D) and one eye with post LASIK ectasia had no statistical change six months after cross-linking (Kmax change +0.08D).

Table 3: Behavior of Kmax in Post LASIK Ectasia Eyes at one year (patient average age 58.2 years)

	1 month	3 months	6 months	1 year
Kmax				
Decrease(better)	3(33.3%)	1(11.1%)	3(60%)	3(60%)
Increase(worse)	4(44.4%)	5(55.6%)	2(40%)	2(40%)
Same	2(22.2%)	3(33.3%)		

Note: Same=Five measurement Kmax average is within 0.678D or pre-operative average

Table 4: Behavior of Kmax in Virginal Keratoconic Eyes

	1 month	3 months	6 months	1 year
Kmax				
Decrease(better)	10(29.4%)	13(52%)	15(65.2%)	4(66.7%)
Increase(worse)	13(38.2%)	6(24%)	5(21.7%)	1(16.7%)
Same	11(32.4%)	6(24%)	3(13%)	1(16.7%)

Table 5: Effect of Patient Age on Cross-linking Effect in Virginal Keratoconus Eyes At 6-month Postoperative

	Age under 40	Age at least 40
Kmax		
Decrease(better)	13(76.5%)	2(33.3%)
Increase(worse)	3(17.6%)	2 (33.3%)
Same	1(5.9%)	2(33.3%)

There appeared to be very minimal yet detectable reduction in corneal thickness after cross-linking. The pre-operative and postoperative corneal thickness measurements of the virginal keratoconus group were as follows. Pre-operative minimal pachymetry in the twenty minute group was 468.7+/-29.3 microns and was at six months postoperatively 466.38 +/- 3.94 microns and in the thirty minute group was pre-operatively 464.4 +/28.3 and post-operatively was +/- 462.2 +/- 4.3 microns.

Preoperative maximal anterior equivalent keratometry, Kmax, was 55.3 +- 4.2 D overall, with 55.3+/-4.D in the 20-minute group and 55.5+/3.9D in the 30-minute group.

The Pentacam nuclear scale for detecting and quantifying early cataract formation showed no changes in the eyes of patients followed for cross-linking. Clearly, the purpose of cross-linking is to stop visual loss. There was detectable visual improvement in virginal keratoconus corneas at six months. Some patients who had the cross-linking procedure had other problems that caused visual loss. For example, one patient had bilateral subluxated lenses, and another one had bilateral cataracts. The referring surgeon planned corrective operations after completion of the cross-linking one year follow up period.

Comparing vision in virginal keratoconus treatment groups, the 20-minute exposure eyes improved from an average pre-operative vision of .3535 logMAR (Snellen 20/45.1) to .2791 LogMAR (Snellen 20/38) at six months postoperatively for a visual improvement of -0.0744 log units. In the 30 minute group vision improved from pre-operative .4044 LogMAR (Snellen 20/50.7) to .3175 log-MAR (Snellen 20/40.5) for an improvement of -0.0869 log units at six month postoperative.

The small post-LASIK ectasia group improved slowly but had yet to recover pre-operative vision (an average of 0.3088 LogMAR 20/40.5) compared to an average vision at the one year follow up evaluation [0.419 LogMAR (20/52.9)]. The average age of the post-LASIK ectasia group was 58.2 years compared with an average age of 34.5 years for the virginal keratoconus patients. Combination of data from the post-LASIK group and other smaller groups diminished the overall average visual change, with vision changing from a preoperative average of 0.3394 LogMAR (Snellen 20/43.7) to a six-month postoperative average of 0.3546 LogMAR (Snellen 20/45.25)

Age was also a factor in the cross-linking effectiveness in the virginal keratoconus eyes with 76.5% of eyes in patients under age 40 actually have corneal flattening as compared to only 33.3% of eyes in patients over age 40. Table 5 presents the details on that subject. One patient with post-LASIK ectasia had only slight improvement in Kmax yet a 6.4 diopter change in refraction due to flattening of most of the central cornea. Figure 1 shows the change in corneal curvature caused by cross-linking in this patient.

Discussion

The patients enrolled in our study had experienced worsening of their keratoconus and post-LASIK ectasia prior to recruitment. Results from our clinical study, which is still in progress, indicate that corneal collagen cross-linking provides stabilization and partial reversal of the corneal irregularity resulting from keratoconus and post-LASIK ectasia. We also used cross-linking to stabilize corneas with keratoconus that had prior intracranial ring segments, and we used it as well for previously transplanted corneas where initial good vision had gradually declined from residual keratoconus in the host tissue.

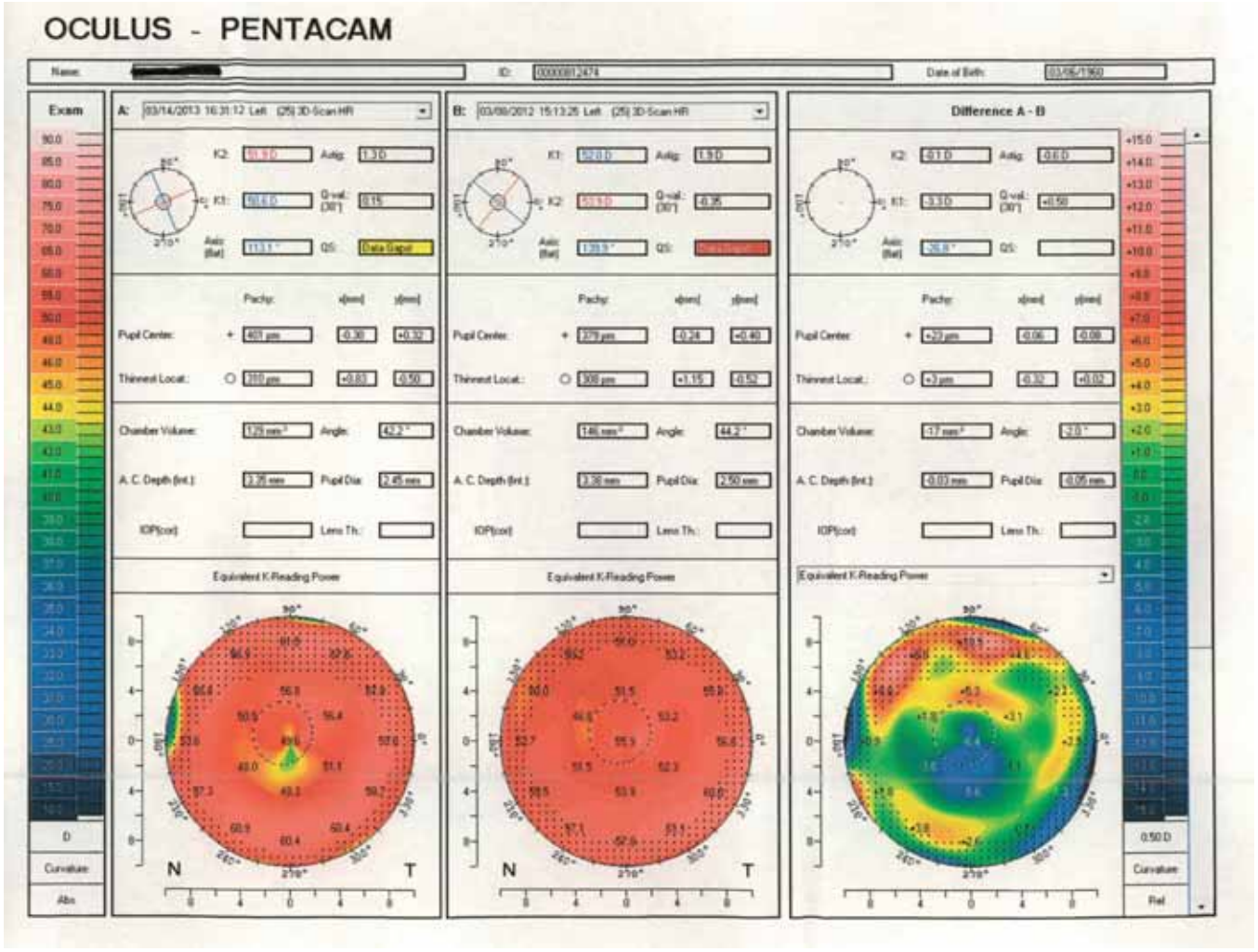

Figure 1. Pentacam HR comparative topometric map of the anterior corneal curvature. At left are the postoperative contour maps. In the middle is the pre-operative map. The subtraction is shown at right. A significant change has occurred that has markedly improved the patients' unaided and spectacle corrected vision.

The results of cross-linking are quite variable both with respect to which patients have the desired effect and also in the uniformity of the effect on parts of the cornea. Thus far, we lack predictors of which corneas will respond and whether additional treatment may be helpful. Generally the changes in curvature are toward more uniformity of curvature, but not always.

We noted good, but imperfect correlation in the effectiveness of cross-linking between two eyes of the same patient. The measure of Kmax is very useful in determining whether a keratoconic or post-LASIK ectasia cornea has worsened, but the Kmax metric does not always speak to the actual power of the cross-linking effect as in the patient illustrated in Figure 1. Two of the most highly responsive corneas have been from people who were genetically either completely or partially African.

Because there is significant variability in the response to cross-linking, it would seem prudent to refrain from combine cross-linking with laser vision correction in the same operation until there is a way to predict the outcome of cross-linking. However, outside of clinical studies to determine the effect of cross-linking alone, combining cross-linking with insertion of intracranial ring segments is recommended.

The more vigorous response in younger eyes is not surprising. This observation only underscores the fact that cross-linking as treatment to reverse or stabilize keratoconus should be employed while patients are young.

The largest published study to date is by Vinciguerra et al. Their series of cross-linking of 401 eyes with data lasting as much as 4 years and with 53.5% of patients with one year or more of follow up, shows stabilization and some reversal of corneal curvature in patients under age 40 with visual improvement and shows stabilization with no aver-

age functional visual improvement on for patients over age 40. They publish on simK data rather than Kmax and sim K continues to decrease over a twenty four month period. They state that their results are best in the age range of 18 to 39 with lesser in the over 40 group possibly because age has already cross-linked the eyes and in the younger group because of the aggressiveness of the disease. These findings are not at odds with the findings of our younger study.

Our study is in its early stages at this point. We anticipate increased patient enrollment and extended follow up of all individuals, which should enable us to achieve greater statistical significance of the results.

Authorship statement
Both authors contributed equally.

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References

1. Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. *Br J Ophthal* 2000;84:834–6.
2. Kumar, Vinay. Eye: Cornea, Degenerations and Dystrophies. *Robbins Basic Pathology* (8th ed.). Philadelphia: Saunders/Elsevier, 2007. ISBN 978-1416029731.
3. Saidel MA, Paik JY, Garcia C, et al. Prevalent of sleep apnea syndrome and high-risk characteristics among keratoconus patients. *Cornea*. 2012;31:600-3.
4. McMonnies CW, Quo vadis older keratoconus patients? Do they die at younger ages? *Cornea*. 2013;32:496-502.
5. Jafri B, Lichter H, Stulting RD. Asymmetric keratoconus attributed to eye rubbing. *Cornea* 23:560–4.
6. Koenig SB. Bilateral recurrent self-induced keratoconus. *Eye Cont Lens* 2008;34:343–4.
7. Chan CC, Sharma F, Wachler BS. Effect of inferior-segment Intacs with and with C3-R on keratoconus" *J Cataract Refract* Surg 2007;33:75-80.
8. Randleman JB, Woodward M, Lynn MJ, et al. Risk assessment for ectasia after corneal refractive surgery. *Ophthalmology* 2008; 115:37-50.
9. Reinstein DZ, Archer TJ, Gobbe M. Stability of LASIK in topographically suspect keratoconus confirmed non-keratoconic by Artemis VHG digital ultrasound epithelial thickness mapping: 1-year follow-up. J Refract Surg. 2009;25:569-77.
10. Schweitzer C, Rogert CJ, Mahmoud AM, et al. Screening of forme fruste keratoconus with the ocular response analyzer. Invest *Ophthalmol Vis Sci* 2010; 51:2403-10.
11. Saad A, Gatinel D, Topographic and tomographic properties of forme fruste keratoconus corneas. *Invest Ophthalmol Vis Sci* 2010 Nov;51(11):5546-55.
12. Ambrosio R Jr, Caiado AL, Guerra FP, et al. Novel pachymetric parameters based on corneal tomotraphy for diagnosing keratoconus. *J Refract Surg* 2011;27:753-8.
13. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. *J Cataract Refract Surg*. 2012;38:2167-83.
14. Fukuda S, Yamanari M, Lim Y, et al. Keratoconus Diagnosis Using Anterior Segment Polarization-Sensitive Optical Coherence Tomography. *Invest Ophthalm Vis Science*, 2013;54:1385-91.
15. Kozomara B, Bohač M, Potkonjak E, et al. Prevalence of keratoconus in candidates for refractive surgical procedures. *Scr Med* 2012;43:25-7.
16. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res* 1998;66:97-103.
17. Zhang Y, Mao X, Schwend T, et al. Resistance of corneal RFU-VA-cross-linked collagens and small leucine-rich proteoglycans to degradation by matrix metalloproteinases *Invest Opthalmol Vis Sci* 2013; IOVS 12-11277v1.
18. Dudakova L, Liskova P, Trojek T, et al. Changes in lysyl oxidase (LOX)distribution and its decreased activity in keratoconus corneas*, Exp Eye Res* 2012;104:74-81.
19. Martins SA, Combs JC, Noguera G, et al. Biomechanical evidence of the distribution of cross-links in corneas treated with riboflavin and ultraviolet A light. *J Cataract Refract Surg* 2006;32:279-83.
20. Wollensak G, Spoerl E, Wilsch M, et al. Keratocyte apoptosis after corneal collagen cross-linking using riboflavin/UVA Treatment. *Cornea* 2004 ;23:43-9.
21. Baiocchi S, Mazzotta C, Cerretani D, et al. Corneal cross-linking: riboflavin concentration in corneal stroma exposed with and without epithelium. J Cataract Refract Surg. 2009;35:893-9.
22. Ostacolo C, Cafuso C, Tronimo D, et al. Enhancement of corneal permeation of riboflavin 5'-phosphate through vitamin E TPGS: a promising approach in corneal trans-epithelial cross linking treatment. Int J Pharm 2013; 440:148-53.
23. Martins SA, Combs JC, Noguera G, et al. Antimicrobial efficacy of riboflavin/UVA combination (365 nm) in vitro for bacterial and fungal isolates: a potential new treatment for infectious keratitis. Invest Ophthalmol Vis Sci. 2008;49:3402-8.
24. Hafezi F, Dejica P, Majo F. Modified corneal collagen cross-linking reduces corneal oedema and diurnal visual fluctuation in Fuchs dystrophy. *Br J Ophthalmol* 2010;94:660-1.
25. Koller T, Iseli HP, Hafezi F, et al. Scheimpflug imaging of corneas after collagen cross-linking. *Cornea*. 2009;28:510-5.
26. Epstein RL, Chiu YL, Epstein GL. Pentacam HR Criteria for Curvature Change in Keratoconus and Postoperative LASIK ectasia. *J Refract Surg*. 2012:28:890-4.
27. Vinciguerra R, Romano MR, Camesasca FL, et al. Corneal Cross-Linking as a Treatment for Keratoconus: Four-Year Morphologic and Clinical Outcomes with Respect to Patient Age. *Ophthalmology* 2013 Epub prior to print January 2013.

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CASE REPORT

Subcutaneous Emphysema and Pneumomediastinum Following a Dental Filling Procedure

Dimitry Voronov
Alyson Russo
Sangeeta Juloori
Sajan Thomas

Vanguard MacNeal Hospital
Department of Internal Medicine
Berwyn, IL 60402, USA

Correspondence
Dimitry Voronov
Internal Medicine Residency Program
3249 S. Oak Park Ave.
Berwyn, IL 60402, USA
dimitryvoronov@students.rossu.edu

ABSTRACT
We report a patient who underwent a routine dental procedure and developed subcutaneous emphysema (SCE) and pneumomediastinum (PM). Clinical management included oxygen therapy, pain control, rest and supportive therapy as needed. Our patient clinically improved with this treatment, and was discharged home two days later. It is important to be aware that even minimally invasive dental procedures can lead to SCE and PM.

KEY WORDS
Dental procedure, subcutaneous emphysema, pneumomediastinum.

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Accepted: April 18, 2013

A 38-year-old female presented to the Emergency Department (ED) with shortness of breath, left-sided facial swelling, and pain on the left side of her neck and face. She was unable to fully open her mouth. She also had blurring of vision in her left eye, and decreased hearing in her left ear. One day prior to her arrival at the ED, she underwent a dental filling procedure on a left maxillary molar. She denied undergoing an endodontic treatment or extraction. She reported some swelling in her face immediately after the procedure. At the dentist's office, the swelling was attributed to an allergic reaction to the injected local anesthetic. However, she reported no known allergies. She was prescribed oral penicillin, and she returned home. Later that night, the swelling worsened, and the patient experienced shortness of breath along with increasing pain in her face and neck. She was subsequently taken to the ED for further evaluation.

Physical examination revealed an alert, afebrile, normotensive patient, who saturated well with a non-rebreather mask. She was noted to have left periorbital, facial, submandibular and anterior cervical edema, with mild crepitus and tenderness over the left temporal bone and cheek. Examination of her ears revealed clear external canals and gray tympanic membranes bilaterally. She had minimally decreased hearing on her left side compared with the right. Her oropharynx was non-erythematous, without signs of infection or gingival complications; however, she was unable to fully open her mouth because of the pain. She was tender to palpation over the left upper chest, and the same painful sensation was elicited by left upper extremity movement. Also, her lungs were grossly clear on bilateral auscultation.

Laboratory studies showed a white blood cell count of 9,900/mm^3, with a normal differential. An EKG showed normal sinus rhythm. The troponin levels were also within normal limits. A chest X-ray revealed a normal cardiac silhouette with clear lung fields. The head and chest computed tomography (CT) revealed gas in left temporal, preorbital and perimandibular areas, which extended down the left neck to the upper mediastinum (Fig. 1-3).

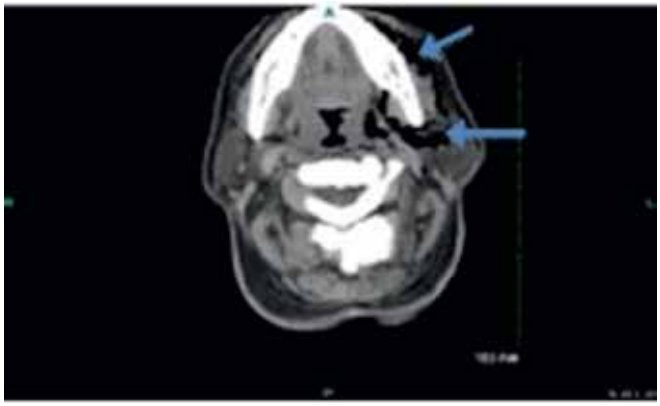

Figure 1. CT scan of the head, showing perimandibular subcutaneous emphysema (arrows).

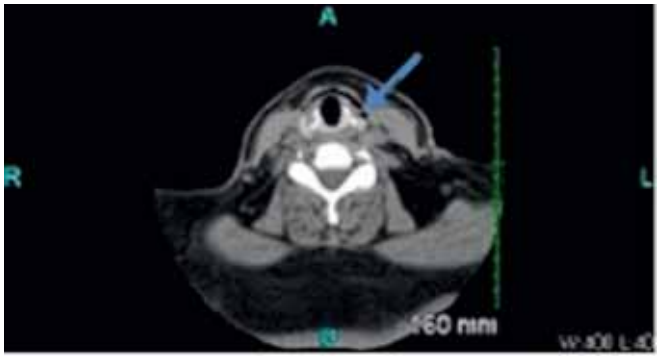

Figure 2. CT scan of the neck, showing peritracheal subcutaneous emphysema (arrow).

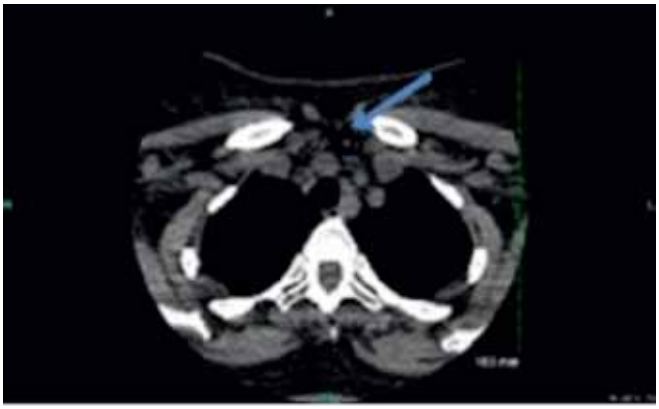

Figure 3. CT scan, showing pneumomediastinum (arrow).

The patient was started on prophylactic ampicillin/sulbactam, and remained on a 100% non-rebreather mask for the next day; she was then slowly weaned off the oxygen. She received acetaminophen/hydrocodone for pain relief. Because the patient complained of difficulty swallowing solid foods as her diet was advanced, a gastrografin swallow study was performed but showed no esophageal perforation. The facial swelling and breathing difficulty improved over the hospital course, and the patient was discharged home on oral antibiotics two days after admission.

Discussion

Spontaneous pneumomediastinum (PM) classically occurs in the setting of increased intra-alveolar pressure, leading to alveolar rupture and diffusion of air into the mediastinum via vascular sheaths.[1] Common triggers include asthma attacks or prolonged Valsalva. Less commonly, invasive dental procedures such as dental extractions or endodontic treatments can trigger PM. Numerous case reports describe subcutaneous emphysema (SCE) and PM after dental extractions of mandibular molars.[2-4] Molars are in close proximity to the submandibular, sublingual, pterygomandibular and retropharyngeal spaces. The proposed mechanism is the introduction of air into these spaces via pressure appliances such as commonly used air-turbine drills – causing PM via diffusion.

We have described a case in which SCE and PM developed from a dental filling procedure of a maxillary molar. Although air-turbine drills are frequently used in both procedures; routine dental fillings typically involve only the enamel and dentin layers of the teeth, whereas endodontic treatments include the deeper pulp. This case emphasizes the propensity of dental procedures to cause SCE and PM, regardless of the type of procedure or the location of the affected tooth. One should consider SCE and PM in patients with a similar presentation following any dental procedure, irrespective of its invasiveness. The treatment for PM includes initial oxygen therapy, analgesia, and rest.[5] Prophylactic antibiotics can also be added to prevent mediastinitis. This treatment, in our patient, contributed to a satisfactory outcome.

Authorship statement

DV gathered patient history and participated in the writing and organization of the case report. AR gathered patient history and treated the patient during hospitalization. SJ contributed to the writing of the manuscript. ST participated in the design, supervision and final approval of the submitted manuscript. DV, AR, SJ and ST all contributed to the final critical revision of this manuscript.

Financial disclosure

The authors declare no conflict of interest involved with this case study.

References

1. Macklin CC. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: clinical implications. Arch Intern Med 1939;64:913.
2. Döngel I, Bayram M, Uysal IO, et al. Subcutaneous emphysema and pneumomediastinum complicating a dental procedure. Ulus Travma Acil Cerrahi Derg 2012;18:361-3.
3. Afzali N, Malek A, Attar AH. Cervicofacial emphysema and pneumomediastinum following dental extraction: case report. Iran J Pediatr 2011;21:253-5.
4. Sood T, Pullinger R. Pneumomediastinum secondary to dental extraction. Emerg Med J 2001;18:517-8.
5. Macia I, Moya J, Ramos R, et al. Spontaneous pneumomediastinum: 41 cases. Eur J Cardiothorac Surg 2007;31:1110-4.

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CASE REPORT

Atypical Form of Congenital Excavated Anomaly of the Optic Disc With Characteristics of Peripapillary Staphyloma and Morning Glory Anomaly

Bojana Markić
Milka Mavija
Emira Ignjatić

Clinic of Ophthalmology, Clinical Center Banja Luka, 78 000 Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Correspondence
Bojana Markić, MD
Department of Ophthalmology, Clinical Center Banja Luka
12 beba, 78 000 Banja Luka
Republic of Srpska, Bosnia and Herzegovina
email: zbmarkic@gmail.com

ABSTRACT
We present a 51-year-old female with a unilateral congenital excavated optic disc anomaly. After clinical examination and appropriate diagnostic procedures we were unable to determine with certainty whether it is a morning glory anomaly or a peripapillary staphyloma. The atypical finding was an optic disc with characteristics of both states. The affected eye had almost normal visual acuity (0.9 Snellen chart), which is a rare finding in congenital anomaly of the optic disc. Confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph, HRT 3.0) was not of diagnostic value in comparison with optical coherence tomography (OCT).

KEY WORDS
Peripapillary staphyloma, morning glory, optic disc anomaly, optical coherence tomography, confocal scanning laser ophthalmoscopy (HRT 3.0).

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A 51- year-old Caucasian woman with no visual complaints went to her local ophthalmologist for an eye examination after developing peripheral paresis of the left facial nerve. Cranial CT findings were within the normal range, and an ENT specialist found no abnormality. With the exception of peripheral facial nerve paralysis, neurological findings were normal.

The patient's best-corrected visual acuity was OD: 0.9 and OS: 1.0 distance (Snellen chart) and Jaeger 1 near for both eyes. Her color vision, external examination, slit lamp biomicroscopy, intraocular pressures, and motility were all normal in both eyes. Funduscopic examination was normal in the left eye with an optic nerve cup to disc ratio of 0.2-0.3. Dilated funduscopic examination of the right eye showed significant excavation on the posterior globe, in which the optic disc was hardly recognizable. It had a poorly visible temporal border and the appearance of hyperpigmentation at the 12 o'clock position of the excavation. Blood vessels radiating from the papillary region seemed to be increased in number and appeared tortuous in the center of the excavation. The macula and periphery were normal (Figure 1).

Figure 1. Patient's right optic disc

A deep excavation was noted on an ultrasonography B-scan of the right eye. Automated perimetry showed an enlarged blind spot and a relative superior altitudinal defect on the right and a full field on the left. Optical coherence tomography (OCT) revealed a deeply seated right optic nerve and the depth of staphyloma was measured 1,2 mm. Retinal pigment epithelium showed significant atrophic changes (Figure 2). OCT of the left optic disc showed it to be normal.

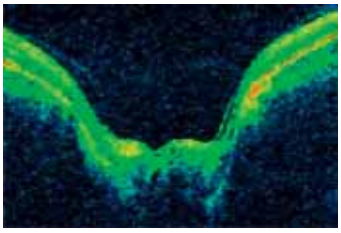

Figure 2. OCT showed a deeply seated right optic nerve

An examination of both eyes was also performed with HRT 3.0, and analysis of the left eye was completely normal. There was a problem in setting the contour line on the right eye due to the decreased visibility of the optic disc. Using the funduscopic picture of the right eye, we placed the contour line as precisely as we could. Stereometric analysis showed an enlarged disk area (3.20 mm^2) as well as an enlarged rim area (3.20 mm^2), so that the Cup/Disc area ratio was 0.00. Moorfields Regression Classification was within normal limits for all segments (Figure 3). Glaucoma probability score classification (GPS) was not classified, because the GPS model was not compatible with the shape of this optic nerve head.

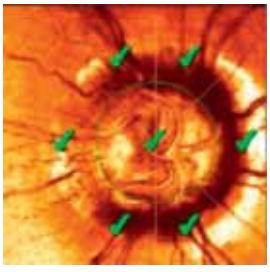

Figure 3. Moorfields Regression Classification on HRTwas within normal limits globally and in all segments

After completion of all diagnostic procedures, we concluded that this atypical optic disc is a congenital anomaly, most likely mild form. Its adequate function was confirmed by the fact that the patient had almost normal visual acuity. However, we were unable to determine with certainty whether the anomaly is a peripapillary staphyloma or a morning glory anomaly, because the atypical optic disc had characteristics of both conditions.

Discussion

Congenital excavated optic disc anomalies include optic disc coloboma, morning glory disc anomaly, peripapillary staphyloma, megalopapilla, and optic pit. These are all extremely rare conditions, which are most commonly are found in early childhood when they cause decreased vision, strabismus and nystagmus. In both morning glory disc anomaly and peripapillary staphyloma, an excavation of the posterior globe surrounds and incorporates the optic disc. Usually, these conditions are associated with unilateral appearing. Visual acuity in the involved eye may be minimally or severely affected, depending on the extent of lesion. These disc anomalies may be associated with other congenital disorders of the eye; often they accompany central nervous system malformations[1] or renal hypodysplasia, where they are part of an autosomal dominant condition called renal coloboma syndrome (RCS) or papillorenal syndrome[2]. In addition, these optic disc anomalies may be associated with retinal detachment, retinochisis, macular edema, choroidal neovascularisation and lipid exudation. Rarely are they associated with the optic disc contractility[3].

In peripapillary staphyloma the area around the disc is deeply excavated, with atrophic changes in the retinal pigment epithelium. The disc remains well-defined, relatively normal in appearance with an absence of glial and vascular anomalies[1]. As opposed to the morning glory disc anomaly, the blood vessels in the peripapillary staphyloma lesion have a normal pattern[4]. Unlike other excavated optic disc anomalies, peripapillary staphyloma is rarely associated with other congenital defects or systemic diseases[5].

Morning glory disc anomaly has a less deep funnel-shaped excavation, along with a grossly anomalous, poorly defined optic disc, including a white tuft of glial tissue that covers the central portion of the cup. Blood vessels appear to be increased in number and emanate from the edge of the disc. After arising from the disc, the vessels turn sharply at the edge of the cup and follow an abnormally straight pattern within the peripapillary region[1].

In our case, optic disc was poorly defined, deeply seated at the bottom of the excavation, without central tuft of glial tissue and with blood vessels abnormal according to the number and arrangement. Due to the atypical form of this optic disc which has the same qualities of peripapillary staphyloma and morning glory anomaly, problem appeared in establishing the diagnosis between these two conditions.

We used two important diagnostic tools for structural analysis of the optic disc: optical coherence tomography (OCT) and confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph, HRT, 3.0)[6].We were interested in establishing their ability to distinguish optic disc head, as in our case, from a normal optic disc. OCT showed significant atrophic changes in retinal pigment epithelium and structural changes most similar to those in peripapillary staphyloma. In contrast, HRT 3.0 showed poorly ability to detect structural changes on this atypical disc.

In summary, this case presents an atypical optic disc with characteristics of both peripapillary staphyloma and morning glory anomaly. An accurate diagnosis is still unclear. Because we found no other ocular or systemic congenital disorders usually associated with morning glory disc anomaly, we believe that the malformed optic disc presented in our case is likely a variant of peripapillary staphyloma. The retention of good visual acuity by our patient is rare in cases like this, so we believe that it is a mild

form . Our findings of visual field, coupled with results from ultrasonography and OCT are important for understanding the structure and function of the optic nerve like this as well as for further monitoring. Finally, we assert that HRT 3.0 is not useful for differentiation of abnormal from normal optic discs in cases like this.

Contributors

BM has performed examination of anterior segment, ultrasound, examination of color vision, analysis of visual field test and HRT examination. MM has performed OCT examination and was consultant on writing this article. EI has performed dilated funduscopic examination and made fundus photography.

Conflict of interest

We declare that we have no conflicts of interest.

References

1. Brodsky MC. Congenital optic disc anomalies. In: Yanoff M, Duker JS, eds. Ophthalmology. 3rd ed. Philadelphia: Mosby; 2009:956-9.
2. Schimmenti LA. Renal coloboma syndrome. Eur J Hum Genet 2011;19:1207-12.
3. Sawada Y, Fujiwara T, Yoshitomi T. Morning glory disc anomaly with contractile movements. Graefes Arch Clin Exp Ophthalmol 2012; 250:1693-5.
4. Kim SH, Choi MY, Yu YS, et al. Peripapillary Staphyloma: Clinical Features and Visual Outcome in 19 cases. Arch Ophthalmol 2005; 123:1371-6.
5. Blair M P, Blair N P, Rheinstrom S D. *et al*. A case of peripapillary staphyloma. Arch Ophthalmol 2000;118:1138–9.
6. Yang B, Ye C, Yu M, et al. Optic disc imaging with spectral-domain optical coherence tomography: variability and agreement study with Heidelberg retinal tomography. Ophthalmology 2012; 119:1852-7.

Atipični oblik kongenitalne ekskavacije optičkog diska s karakteristikom peripapilarnog stafiloma i *morning glory* anomalije

APSTRAKT

Prikazan je slučaj 51-godišnje pacijentice sa unilateralnom kongenitalnom anomalijom optičkog diska. Kliničkim pregledom i učinjenim dijagnostičkim pretragama nije se moglo sa sigurnošću utvrditi da li se radi o peripapilarnom stafilomu ili o morning glory anomaliji optičkog diska zbog atipičnog javljanja papile sa karakteristikama oba stanja. Ustanovljena je gotovo normalna vidna oštrina zahvaćenog oka (0,9 kuke po Snellen-u), što je izuzetno rijedak nalaz u slučaju sa prisutnom kongenitalnom anomalijom optičkog diska poput ove. Konfokalna skening laser oftalmoskopija (Heidelberg Retina Tomograph, HRT 3.0) se nije pokazala od dijagnostičkog značaja u ovom slučaju, za razliku od optičke koherentne tomografije (OCT).

KLJUČNE REČI

Peripapilarni stafilom, morning glory anomalija, optička koherentna tomografija, konfokalna skening laser oftalmoskopija (HRT 3.0)

UDK 616.24-006.04-074

IMAGES IN CLINICAL MEDICINE

Dual Pulmonary Infections In a 57-Year-Old Male With Large Adrenal Mass

Jennifer L. Bero

Pathology Department
University of Illinois -
Stroger Hospital of Cook County
Chicago, IL 60612 USA

Correspodence
Jennifer L Bero, MD
Pathology Department
Stroger Hospital of Cook County
Chicago, IL 60612 USA
E-mail: jbero@tds.net

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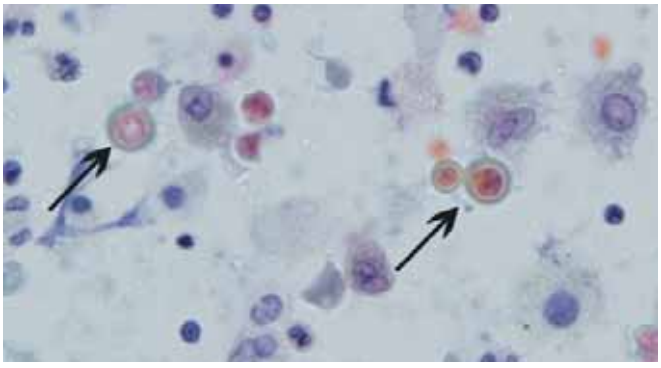

Figure 1. High power photomicrograph showing *Blastomyces* with broad based budding (arrows).

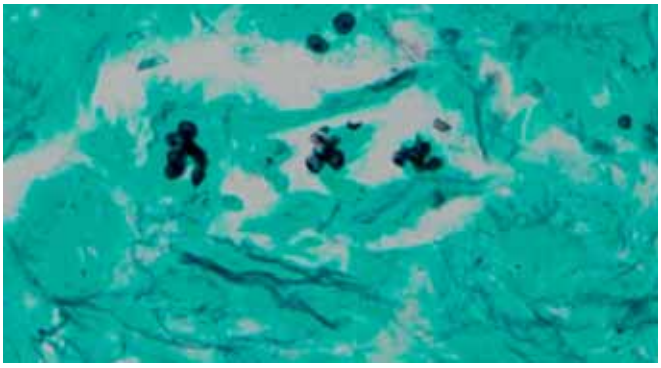

Figure 2. A GMS stain of the lung nodule demonstrating *Pneumocystis jiroveci*.

A 57-year-old male presented with complaints of progressive dry cough, fever, headaches and weight loss, suggesting a pulmonary infection and/or possible malignancy. Bronchial washings from the area of consolidation revealed broad-based budding yeast consistent with *Blastomycosis* (Figure 1). The CT scan showed two nodules in the right lung that might be malignant. Biopsy of one nodule showed *Pneumosystis jiroveci* (Figure 2).

Blastomycosis and pneumocystis jiroveci pneumonia are both opportunistic infections most often seen in immunosuppressed patients. This individual had no known medical condition to cause immuno-suppression.

A CT scan of the chest showed consolidation of the left lung indicating possible pneumonia (Figure 3, double arrows).Abdominal imaging demonstrated a large adrenal mass (Figure 3, single arrow). Serum and 24-hour urine cortisol levels were significantly elevated. These findings are consistent with a cortisol-producing adrenal tumor. The left adrenal mass was surgically removed, and the diagnosis of a cortisol producing adreno-cortical carcinoma was confirmed.

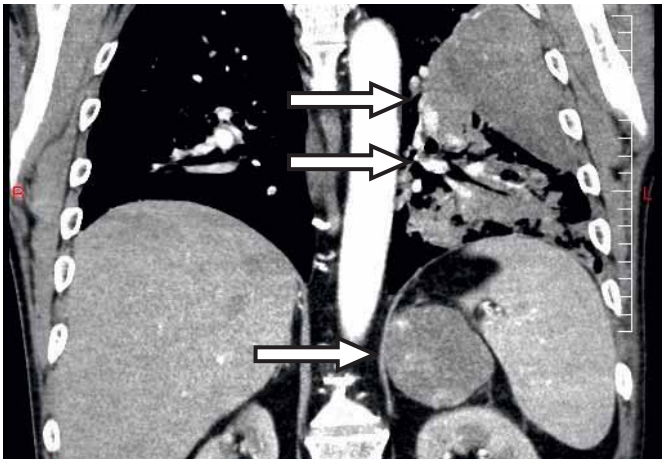

Figure 3. A CT scan demonstrating the left adrenal gland mass (single arrow) and consolidation of the left lung (double arrows).

We conclude that a cortisol-producing adrenal cortical carcinoma caused systemic immuno-suppression that resulted in a dual pulmonary infection with Pneumoncystis jiroveci and Blastomyces. The pulmonary infections resolved upon removal of the adrenal mass.

UDK 616.126-089

LETTER TO THE EDITOR

Trans-Apical Trans-Catheter Aortic Valve Implantation: The Berlin Experience

DOI: 10.7251/SMD1301031C *(Scr Med 2013;44:31)*

In the latest edition of Scripta Medica, *D'Ancona et al* gave a comprehensive review of trans-apical trans-catheter aortic valve implantation (TAVI). Their impressive results obtained within a short period of time involved a large cohort of patients.[1] The German experience with this new technology differs from most other centres world wide in that there have been no limitations of procedural funding and patient choice. Consequently, over 30% of all aortic valve interventions performed use TAVI technology.

For any unit setting up a TAVI program, the main point is the need for a multi-disciplinary heart team to facilitate optimal patient selection. This is key to achieving successful outcomes for both the short and longer terms. It is the responsibility of this heart team to determine an individual patient's risk from previously identified variables independently associated with mortality and poor treatment response,[2] as well to oversee a systematic anatomical work up from access site to implantation site.

What does TAVI offer over surgical AVR? There is no doubt that, in the majority of cases, surgical AVR is a successful procedure supported by robust long-term follow-up data. However, the less invasive TAVI offers a number of advantages, not the least of which is procedural recovery within a matter of days, often with immediate symptomatic improvement. Indeed, the two year PARTNER outcome follow-up data comparing TAVI with surgical AVR continues to show the benefits of TAVI.[3]

What does the future hold for TAVI? We anticipate further development with regard to patient selection in which imaging modality affords optimal anatomical assessment of the aortic valve complex and peripheral vasculature. Technology will continue to develop the minimally invasive approach, which is the biggest advantage of TAVI over surgical AVR. Consequently, a 'trans-apical approach may be used less frequently than retrograde trans-femoral access in all but the minority of patients. In patients where femoral access is borderline, use of other access sites (axillary, subclavian and direct aortic [trans-aortic]) will become routine. Delivery technology will continue to improve with further reductions in calibre; this will lessen vascular access site bleeding. Finally, the first-generation re-positional valves now under evaluation, and second-generation valves with sealing skirts, will help to reduce the extent of para-valvular AR. Procedural changes will develop as well. For example, all retrograde trans-femoral TAVI, trans-aortic and subclavian cases in our centre are performed under conscious sedation. This eliminates the potential risks associated with general anaesthesia in our elderly patient cohort.

If the accumulated long-term data show continued superiority of TAVI over surgical AVR, this promising technology will likely be extended to lower risk patients. Indeed, as mentioned by *D'Ancona et al,* SURTAVI and also the UK TAVI trial will shortly begin evaluating this group; both trials are currently recruiting.[4]

There is no doubt that TAVI is here to stay. In time it may well have as much of an impact on the treatment of symptomatic aortic stenosis as angioplasty and stent insertion has had on symptomatic angina pectoris.

Dr. James Cockburn
Sussex Cardiac Centre, Brighton, UK

References

1. D'Ancona G, Pasic M, Drews T, et al. Transapical transcatheter aortic valve implantation: The Berlin experience. *Scr Med* 2012;43:79-84.
2. Thomas M, et al. Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation 2010;*122:62–9.
3. Kodali SK, Williams MR, Smith CR, et al. PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686-95.
4. www.clinicaltrials.gov

UDK 616-089.843-06

LETTER TO THE EDITOR

On Keratoconus Incidence in Prospective Refractive Surgery Patients

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Dear Editor,

We read with interest the article, "Prevalence of Keratoconus in Candidates for Refractive Surgical Procedures," and we congratulate the authors, Kozomara et al.[1] on their important work. The fact that there was such a high prevalence of keratoconus among their patients, a prevalence far above that of the normal population, underscores the need for a high index of suspicion of keratoconus when seeing patients for elective surgery. The advanced Scheimpflug technology that the authors used must have been helpful in detection of keratoconus.

In patients where keratoconus is suspected, and who avoid use of contact lenses for two weeks, collection of baseline data with five Scheimpflug scans per eye will allow for even more rapid detection of change in the corneal curvature with time.[2] Some cases of keratoconus, initially considered to be unilateral, end up showing progressive curvature change with time. Crosslinking, a safe and highly effective procedure for the stabilization and partial reversal of keratoconus[3], is certainly indicated in cases of keratoconus with progression and also for individuals under age 18 with keratoconus even before there is evidence of progression.[4,5] After crosslinking is complete, some of these keratoconus patients may be candidates for intra-corneal rings; a few may be candidates for subsequent partial surface excimer laser correction of astigmatism with continued follow up.

Robert L. Epstein, MD
Greg L. Epstein, BS
Mercy Center for Corrective Eye Surgery
McHenry, Illinois, USA
rlepstein@aol.com

References

1. Kozomara B, Bohač M, Potkonjak E, et al. Prevalence of keratoconus in candidates for refractive surgical procedures. *Scr Med* 2012;43:25-7.
2. Epstein RL, Chiu YL, Epstein GL, et al. Criteria for curvature change in keratoconus and postoperative LASIK ectasia. *J Refract Surg* 2012;28: 890-4.
3. Koller T, Mrochen M, Seiler T. Complications and failure rates after corneal crosslinking. *J Cataract Refract Surg* 2009;8:1358-62.
4. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of corneal collagen cross-linking in children and adolescents. *J Refract Surg* 2012;28:753–8.
5. Randleman JB. Corneal Collagen Cross-linking: New and expanding applications. *J Refract Surg* 2012;28:744-5.

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LETTER TO THE EDITOR

Burnout Syndrome Among Residents of Family Medicine

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Dr. Stanetić et al.[1] studied burnout syndrome among residents in Family Medicine, using the Maslach Burnout Inventory, a well-known questionnaire. Using this method, they assessed the influence of gender, marital status, and number of children in the families of participants and reported that 77% of the respondents had high level of stress.

However, in similar studies,[2] severe burnout syndrome (also measured using the Maslach Burnout Inventory) was reported in about 50% of critical care physicians. Those who work in Intensive care units (ICU) also have a high level of work-related stress, a factor known to increase the risk of burnout syndrome. In addition, physicians who work in the ICU have a high number of working hours including a number of night shifts and limited vacation time.

This syndrome is also prevalent among medical oncologists. Whippen and Canellos[3] surveyed members of the American Society of Clinical Oncology and reported that 56% of participants fulfill the criteria for burnout syndrome. On the contrary, medical students at the University of Sao Paulo exhibited a low prevalence of burnout syndrome (10.3%).[4] Other studies estimate that burnout syndrome affects between 10% and 45% of medical students.[5]

Unexpectedly, severe burnout syndrome that was reported by Stanetić et al affects family practice residents more often than critical care physicians. If the family medicine residents in the Republic of Srpska did not exaggerate their answers, the authors should offer some possible explanations for this discrepancy. Perhaps they should note additional factors that increase burnout syndrome among the family residents, such as vacation time, moonlighting, or other contributing factors. For vacation time, the report should include physicians' satisfaction both with vacation duration (<15 days; 15-30 days; >30 days) and quality (consider vacation time sufficient: *yes* or *no*). Vacation time is an important factor that may prevent/cause burnout at work, not only in physicians and nurses, but in many other workers as well.

Dr. Miroslav Jerinić
Regional hospital Liberec, Husova 10
460 63 Liberec 1, Czech Republic

References

1. Stanetić K , Tešanović G, Burgić-Radmanović M. Sindrom sagorevanja na poslu specijalizanata porodične medicine. *Scr Med* 2011; 42:14-7.
2. Papazian L, Kentish-Barnes NEmbriaco N, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. *Curr Opin Crit Care* 2007;13:482-8.
3. Whippen DA, Canellos GP. Burnout syndrome in the practice of oncology: results of a random of 1,000 oncologists. *J Clin Oncol* 1991;9:1916-20.
4. Costa EF, Santos SA, Santos AT, Melo EV, Andrade TM. Burnout Syndrome and associated factors among medical students: a cross-sectional study. *Clinics* (Sao Paulo) 2012; 67:573–9.
5. Dyrbye LN, Thomas MR, Massie FS, et al. Burnout and suicidal ideation among U.S. Medical students. *Ann Inter Med* 2008;149:334–41.

In Reply

Throughout 2010 we studied the incidence of stress and burnout syndrome among Family Medicine residents. We used three questionnaires: a sociodemographic data questionnaire created for our particular research objectives; a questionnaire for self-assessment of stress and the Maslach Burnout Inventory (MBI) for assessment of the risk of burnout syndrome

Results from the questionnaire for self-assessment of stress level showed that 77% of the participants met the criteria for high level of stress. Results from the MBI questionnaire showed that Family Medicine residents who participated in the survey had a moderate risk of burnout syndrome. The average degree of emotional exhaustion in this cohort was 21.9, a result that falls into the category of moderate risk. The average degree of depersonalization was 7.45, and the average level of personal satisfaction was 39.65, both of which also indicate moderate risk. If we compare the results from the Family Medicine residents in the Republic of Srpska with results obtained from the other studies cited, it seems obvious that the Family Medicine residents had a significantly lower risk of burnout syndrome than the ICU doctors or the oncologists in the US, but not as low as the risk for medical students.[1] The results of our study are similar to those from studies conducted among residents in Lebanon, [2] France [3] and the Netherlands.[4]

Dr. Jerinić's observations about the influence of vacation time and quality on the development of burnout syndrome are important. Our questionnaire did not contain a question about the length of vacation time, because it is an issue defined by the law in our country. The average number of vacation days for the residents is 20 workdays per year. We agree with Dr. Jerinić that the length of vacation time is an important factor that may influence burnout syndrome. A high quality of vacation time may also help to prevent of burnout.

Kosana Stanetić, MD, Ph.D.
Primary Health Centre Banja Luka
Department of Family Medicine
Medical Faculty Banja Luka,
Bosnia and Herzegovina

References

1. Whippen DA, Canellos GP. Burnout syndrome in the practice of oncology: results of a random of 1,000 oncologists. J Clin Oncol 1991;9:1916-20.
2. Ashkar K, Romani M, Musharrafieh U, et al. Prevalence of burnout syndrome among medical residents: expirience of a developing country. Postgrad Med J 2010;86:266-71.
3. Blanchaed P, Truchot D, Albiges-Sauvin L, et al. Prevalence and causes of burnout among oncology residents: A comprehensive nationwide cross-sectional study, Eur J cancer; 2010.
4. Prins JT, Hoekstra-Weebers JE, Gazendam-Donofrio SM, et al. Burnout and engagement among resident doctors in the Netherlands: a national study. Med Educ. 2010;44:236-47.

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SPECIAL ARTICLE-CLINICAL PRACTICE

Risk Factors for Venous Thromboembolism and Duration of Anticoagulation Therapy

***Nebojša M. Antonijević*[1,2]**
***Vladimir Kanjuh*[1,3]**
***Ivana Živković*[2]**
***Ljubica Jovanović*[2]**

[1]*School of Medicine, University of Belgrade*
[2]*Clinic for Cardiology, Clinical Center of Serbia, Belgrade*
[3]*Serbian Academy of Science and Arts, Committee on Cardiovascular Pathology*

Correspodence
Dr. Nebojša Antonijević, Clinic for Cardiology, Clinical Center of Serbia, Pasterova 2, 11000 Belgrade, Serbia
e-mail: drantoni@gmail.com
Cell phone: +381641939785

ABSTRACT
An adequate regimen for prophylaxis of venous thromboembolism (VTE) requires indentification of reversible and irreversible risk factors. Recent data confirm that the greatest number of pulmonary emboli (PE) occur in non-surgical patients. VTE also develops in many surgical patients upon hospital discharge. These findings emphasize the need for adequate VTE prophylaxis in inflammatory diseases, acute medical illness, and other conditions, as well as the need to optimize anticoagulant regimens after surgery. Establishing VTE risk factors, identifying acquired or inherited thrombophylias and occult or previously undiagnosed malignancy will help design an adequate anticoagulant regimen as secondary VTE prophylaxis for surgical and other patients. Follow up measures should include D-dimer values, ultrasonographic assessment of residual venous thrombosis and echocardiographic parameters, along with other relevant clinical data to assess the risk of VTE reoccurrence. These procedures will ensure the optimal duration of individually tailored anticoagulant therapy, with special attention to comorbidities and tendency to hemorrhage.

KEY WORDS
Venous thromboembolism, thromboprophylaxis, recurrent thrombosis, risk for bleeding.

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Venous thromboembolism (VTE) is the third leading vascular cause of mortality after myocardial infarction and cerebrovascular insult.[1] It is the most preventable disorder. Thus improving measures to prevent VTE remains a top clinical priority.[2] Over two-thirds of all symptomatic VTE occur in patients that were not subjected to surgical procedures.[3] It was reported that 47-76% of all clinical VTE events after hip and knee surgery occur after hospital discharge, and it is recommended to extend VTE prophylaxis in such patients.[3,4]

Although venous thromboembolism is often present in surgical patients during the postoperative period, 70-80% of fatal pulmonary emboli (PE) develop in nonsurgical hospital patients. In 40% of such cases, an age factor is associated with other risk factors, such as previous VTE, malignancy, cerebrovascular accident, heart failure, chronic obstructive pulmonary disease, sepsis and immobilization or confinement to bed.[5] The incidence of venous thromboembolism increases with age, ranging between 1/10,000 per year in younger patients and 5-6/1,000 per year in people over 80 years.[5] An increase in VTE-related morbidity correlates with a number of associated comorbidities, such as inflammatory conditions, elevated acute-phase reactants and reduced anticoagulant proteins.[5]

Prevention and treatment of VTE requires key decisions for further management. These include determining the duration of anticoagulant treatment, selection of measures to prevent recurrent venous thromboembolism and VTE sequelae (pulmonary hypertension, post-thrombophlebitic syndrome) as well as appropriate diagnostic screening for thrombophilia and occult malignancy, along with defining reversible and irreversible risk factors for VTE.[6] A number of authors give priority to establishing optimal anticoagulant treatment over detecting possible congenital thrombophilic states that indicate clinical risk factors for VTE.[6]

Classification of risk factors for VTE

The various classifications and categorizations of risk factors for VTE are a mainstay for tailoring the optimal treatment of VTE patients to their individual characteristics.[7]

For example, Kaatz's categorization of VTE is particularly useful: VTE provoked by risk factors, cancer-related, idiopathic, thrombophilia-related and recurrent VTE.[7] Another classification is based on the strength of risk factors for VTE: **strong** risk factors for VTE with odds ratio > 10 include trauma or fracture, major orthopedic surgery, oncology surgery; **moderate** risk factors with odds ratio 2-9 include non-oncology surgery, use of oral contraceptives and hormone replacement therapy, pregnancy and puerperium, hypercoagulability state and previous VTE; **weak** risk factors with odds ratio <2 include advanced age, bed confinement for longer than three days, imobility on long trips, metabolic syndrome and air pollution.[8] The life-style or disease-associated risk factors for arterial and venous thromboembolism include obesity, diabetes mellitus, hypertension and smoking,[8] with special consideration given to the impact of dyslipidemia on VTE occurence. (Commonly known VTE risk factors[4-10] are presented in Table 1.)

Table 1. Risk factors for VTE

Surgery, trauma (major or lower limb trauma)
Immobility, lower limb paresis
Malignancy (active or occult), malignancy therapy (hormonal, chemotherapy, radiation, treatment with angiogenesis inhibitors)
Previous VTE
Use of estrogen-containing contraceptives, hormone-replacement therapy, or selective estrogen receptor modulators, agents stimulating erythropoiesis
Acute medical illness
Inflammatory bowel disease, nephrotic syndrome, myeloproliferative disease, chronic obstructive pulmonary disease, congestive heart failure, paroxysmal nocturnal hemoglobinuria
Dehydration, transfusion
Venous compression (tumor, hematoma, arterial abnormalities)
Obesity, advanced age
Pregnancy and puerperium
Congenital or acquired thrombophilia
Application of central venous catheters

Risk factors for VTE often overlap with those for coronary heart disease (smoking, obesity, high consumption of red meat instead of a healthier diet of fish, fruit and vegetables, psychosocial stress, hypertension). The JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) provides a convincing example of how risk factors for arterial and venous thromboembolism converge. Results of that study showed a reduction in VTE by 43% in the group treated with rosuvastatin (20 mg daily) compared to the control (untreated) group.[9]

Bauer and Previtali[8,10] group the VTE risk factors into **acquired** (including antiphospholipid syndrome, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, inflammatory bowel disease, Wegener granulomatosis, paresis/paralysis of lower extremities, etc.), **inherited** (deficiencies of antithrombin, proteins C and S, factor V Leiden and prothrombin G20210A mutations, disfibrinogenemias) and **mixed** risk factors (hyper-homocysteinemia, resistance to activated protein C in the absence of factor V Leiden mutation, increased activity of factors VIII, IX, XI, thrombin-activated fibrinolysis inhibitor (TAFI), reduction of tissue factor pathway inhibitor (TFPI), and fibrinolytic activity).

Patients heterozygous for factor V Leiden have a three times higher risk for an initial VTE while homozygous individuals carry a 15-20-fold increased risk.[9] Goldhaber considers the combination of homozygous factor V Leiden mutation, double heterozygotes for factor V Leiden and prothrombin G20210A mutation, deficiencies of proteins C, S and antithrombin as well as antiphospholipid syndrome to be a particularly ominous setting for thrombophilia.[9]

Although estrogens in the form of oral contraceptives or postmenopausal hormone therapy are well-known risk factors for VTE, it is interesting to note that the third-generation progestins, dezogestrol and gestodene also rank among risk factors for VTE. [9]

In order to optimize an anticoagulation regimen for patients with VTE, one should establish the importance of their specific VTE risk factors by distribution into these

three categories: 1. Reversible – major (occuring a month after surgery where general anesthesia lasted longer than 30 minutes, hospitalization longer than three days, plaster immobilization of lower limbs); 2. Reversible - minor (hormone replacement therapy, pregnancy and puerperium, an eight-hour or longer flight or travel in a sitting position [a stricter limitation is 4-6 hours] or the presence of major reversible risk factors during 1-3 months); 3. Nonreversible or permanent risk factors for VTE (malignancy, molecular thrombophilias).[11]

Long-term anticoagulant therapy is strongly recommended for patients with persistent nonreversibile risk factors, such as homozygous mutation of factor V Leiden, double heterozygotes for factor V Leiden and prothrombin G20210A mutations, protein C/S deficiency, antiphospholipid antibodies.[11] Interruption of anticoagulant therapy constitutes a greater risk for recurrent VTE in patients with previous proximal deep vein thrombosis (DVT) compared with the distal lower limb DVT.[12]

Agnelli classifies risk factors for VTE as **transient** (surgery, trauma, immobilization) or **persistent** (cancer and paralysis), but considers those individuals with idiopathic and spontaneous VTE to have no identified risk factors for thrombosis. Numerous studies identifed male gender as a risk factor for recurrent VTE [relative risk (RR) 1,6; 95% confidence interval (CI) 1,2-2,0].[13] The observation that the risk of fatal pulmonary embolism is two-three times greater after an episode of PE than after a DVT episode is also of clinical relevance.[13]

Classification based on risk for recurrent VTE

Prandoni[14] defines several groups of risk factors for recurrent VTE: 1) persistent acquired risk factors (active malignancy, especially with metastasis and treated with chemotherapy, patients with chronic nonsurgical diseases who are immobilized for long periods of time), 2) major transient risk factors (previous surgery or trauma), 3) minor transient risk factors (minor trauma, long-haul flights, estrogen therapy, pregnancy and puerperium), 4) spontaneous VTE, 5) congenital thrombophilias (with special emphasis on the deficiencies of proteins C and S and antithrombin, increase of factors VIII and IX, hyper-homocysteinemia). Although recent studies associating recurrent VTE with homozygous factor V Leiden and prothrombin 20210 remain controversial, it is indisputable that patients on one-year anticoagulation therapy regimens have a lower percentage of recurrent VTE than those on conventional three-month anticoagulation regimens. Lowering homocysteine levels with vitamin B12 supplementation does not reduce the risk of recurrent VTE. Prophylaxis of VTE in pregnancy must not be discontinued before the end of the puerperium (6 weeks after childbirth).

Patients with significant transient risk factors should be treated for three months, but the duration of treatment could be less (six weeks) if thrombosis is localized to veins in the lower legs. Patients with minor transient risk factors require treatment tailored to the degree of hemorrhagic risk for each individual.[15] Indefinite anticoagulant treatment is recommended for patients with multiple episodes of VTE. This might include an implanted vena cava filter if anticoagulants are contraindicated as well as for individuals with antiphospholipid syndrome.[14]

Table 1 lists the most important risk factors for recurrence of VTE upon anticoagulant therapy discontinuation.[15] Prospective studies in patients with VTE indicate a greater risk of recurrent VTE in patients who have high levels of D-dimer a month after termination of anticoagulant therapy.[13] Identification of these patients by D-dimer monitoring can single out those at greatest risk and help to prevent recurrent VTE.[14] In the PREVENT trial (Prevention of Recurrent Venous Thromboembolism), one group of patients with spontaneous VTE received anticoagulant (warfarin) therapy for six months, but measurement of D-dimer for seven weeks following warfarin withdrawal showed that those with increased D-dimer levels had a twofold higher recurrence rate.

Table 2. Risk factors for recurrent VTE[15]

When anticoagulation therapy has already been administered
Advanced Age
Immobilization
Malignancy
Chronic obstructive pulmonary disease
Enlargement or dyskinesia of right heart ventricle
After the termination of anticoagulant therapy
Male gender
Body overweight
Signs and symptoms of PE before DVT
Low levels of HDL
Absence of recanalization of lower limbs veins on ultrasound scan

However, a meta-analysis of 1888 patients with spontaneous VTE suggests that the problem is not that simple. That study reported that 3.5% of patients have an annual risk for recurrent VTE despite normal D-dimer levels measured upon discontinuation of anticoagulant therapy.[15] In a separate meta-analysis of idiopathic VTE studies, the recurrence rate was 7.2% for patients who had normal D-dimer values measured one month after discontinuation of anticoagulant therapy. Some reports suggest that elevation of D-dimer one or two months after therapy is associated with significant risk of spontaneous recurrent thrombosis [hazard ratio 2.0, 95% confidence interval (CI) 1.01 to

3.9].[16] The risk of recurrent VTE is 10% per year in men who have had spontaneous VTE with elevated D-dimer, whereas the risk of spontaneous VTE, or VTE caused by defined factors with negative D-dimer, in women is about 2%. Consequently, the benefit of long-term anticoagulant therapy in these women remains vague. [16]

According to Agnelli, the main predictors of recurrent thromboembolism are D-dimer levels and the presence of residual thrombosis.[13] The hazard ratio for recurrent VTE was 2.4 in patients with persistent residual thrombosis (shown by venous ultrasonography) compared with those who had vein recanalization.[13] The same author notes that recurrent VTE can be as high as 29% in patients positive for anti-cardiolipin antibodies after a first episode of VTE compared with 14% of those without the antibodies ($p < 0.01$). The PREVENT study established the efficacy of prolonged anticoagulant therapy in patients with factor V Leiden and prothrombin G20210A mutations by showing that the annual incidence of recurrent VTE was reduced from 8.6% to 2.2% per year.[13]

The Vienna Prediction Model for Recurent VTE identifies the risk of recurrent VTE in relation to sex, clinical presentation and laboratory values of D-dimer.[14,17] Besides the aforementioned risk factors, this model indicates that a number of other abnormalities can be involved, including elevated factor VIII, factor IX, increased hematocrit, low levels of apolipoprotein AI, HDL and vitamin B6, and FSAP Marburg (Marburg I polymorphism of factor VII activating protease), overweight, pregnancy and puerperium, even chronic renal disease, are associated with increased risk for recurrent VTE.[17-27]

Duration of anticoagulant therapy for secondary prophylaxis depends upon the category of VTE

According to Goldhaber,[9] the recommended duration of anticoagulant therapy for a first attack of PE and/or DVT related to an identified risk factor for VTE (surgery, trauma, oral contraceptives, pregnancy, hormone replacement therapy) is from three to six months with a target International Normalized Ratio (INR) 2-3. For patients with a first episode of upper limb DVT or isolated lower leg DVT with identified risk factors, a three-month course of anticoagulant therapy with an INR of 2-3 is advised. For a second attack of VTE provoked by an identified risk factor, most clinicians recommend doubling the duration of anticoagulant therapy; a few of them favor so-called lifelong anticoagulation therapy, or indefinite treatment. The ACCP (American College of Chest Physicians), NCCN (National Comprehensive Cancer Network) and ASCO (American Society of Clinical Oncology) reached a consensus that patients with malignancies should be treated with low-molecular-weight heparin (LMWH) during the first from three to six months and then indefinite anticoagulation therapy (vitamin K antagonists or LMWH). Table 3 shows the recommended duration of anticoagulant therapy for secondary prophylaxis of VTE[15]

Table 3. Optimal duration of therapy for secondary prophylaxis of VTE[15]

CATEGORY OF VTE	GUIDELINES FOR DURATION OF ANTICOAGULANT REGIME
First episode of PE or proximal DVT related to an identified risk factor	3-6 months
First episode of upper-limb DVT or isolated lower-leg DVT related to an identified risk factor	3 months
Second episode of DVT related to an identified risk factor	Uncertain
Third episode of DVT	Indefinite duration
DVT in malignancy	Indefinite duration until malignancy is resolved
Spontaneous PE/ proximal DVT of lower limb	Consider indefinite duration
First unprovoked DVT of calf	3 months
Second unprovoked DVT of calf	Uncertain

Aggressive use of anticoagulant therapy after the first six months of treatment remains debatable. Many physicians continue the standard anticoagulant regimen with a target INR 2-3, whereas others consider a low-intensity anticoagulant regimen with a target INR 1.5-2 to be effective and safe.[15] Three studies achieved a 90% risk reduction in patients with standard anticoagulation therapy and a target INR of 2.5 (range 2-3) with the extended regimen, while a low-dose regimen (INR 1.5-2) resulted in 60% risk reduction.[16] Any decision on anticoagulant therapy cessation in individual patients should take into account that the annual incidence of major bleeding in patients on long-term anticoagulant therapy is 1.5-2%, and that case fatality rate or frequency of major bleeding episodes with fatal outcome is greater than the frequency of recurrent VTE. Consequently, for certain patients with high hemorrhagic risk, unconventional oral anticoagulant therapy with a target INR 1.5 to 2 should be considered.[14]

Persistent dysfunction or right ventricular enlargement after acute PE, residual DVT, non-recanalised DVT (confirmed by venous ultrasonography), low HDL, male sex and body overweight are considered risk factors for recurrent VTE. In contrast, the finding of a persistent thrombus on chest computed tomography (CT) has no predictive value for the recurrence of pulmonary emboli (PE) since about half of PE appear as persistent defects in chest CT recordings six months after the initial event.[9,15] Also, most thrombophilias do not increase the risk of recurrent VTE.[15] Clus-

tered data from 10 studies (3104 patients enrolled with a first episode of VTE) indicate an odds ratio for recurrent VTE to 1.72 (95% CI 1.27 to 2.31) in those with prothrombin mutation G20210A and a ratio of 1.41 (95% CI 1.14 to 1.75) with factor V Leiden mutation.[13] Meta-analyses indicate that the incidence of recurrent VTE is higher immediately after discontinuation of anticoagulant therapy, but it tends to decrease over time. In addition, the onset of recurrent VTE nine months after discontinuation of anticoagulation therapy does not depend on the prior therapy duration.[13]

Recommended duration of primary prophylaxis anticoagulant therapy depends upon VTE category

Based on official recommendations, primary prevention of VTE depends upon the type of previous surgery. In addition to selecting the appropriate type of thromboprophylaxis (mechanical, medication, or combined) and the type and dose of anticoagulant agents, it is necessary to consider the duration of treatment and to tailor it to the specific requirements of a particular surgical procedure. This would apply as well for protection against VTE in nonsurgical ("medical") patients, too. The National Institute for Health and Clinical Excellence (NICE) clinical recommendations (2010) advise thromboprophylaxis over a period of 28-35 days for patients with elective hip surgery or hip fractures and 10-14 days for patients with elective knee surgery, while major surgery for abdominal or pelvic malignancy requires thromboprophylaxis for 28 days from the day of the intervention.[4, 28] American College of Chest Physicians (ACCP) guidelines recommend continuing thromboprophylaxis up to 28 days, continuing after hospital discharge for those with malignancies and for other high-risk patients after general or gynecological surgery. [28]

Thromboprophylaxis is advisable for individuals with reduced mobility, such as those who have had general, gynecologic, urologic, thoracic surgery, coronary artery bypass graft or bariatric surgery as well as those with major trauma or spinal cord injury. It should be continued until the patient has regained mobility, usually about five - seven days.[28]

Where there is lower limb immobilization in a cast, the physician should prescribe the appropriate thromboprophylaxis after evaluating the risk and benefit in each patient.[28] ACCP (2008) recommends thromboprophylaxis for acutely ill patients admitted to the hospital due to congestive heart failure, severe respiratory diseases, and for those who are "bedridden" or who have additional risk factors for VTE, such as: active malignancy, previous VTE, sepsis, acute neurologic disease or inflammatory bowel disease.[28] The ACCP also advises tailoring thromboprophylaxis according to the type of cancer surgery and bedridden patients.[28] The ACCP guidelines from the CHEST 2008 do not recommend pharmacotherapy for prevention of thrombosis caused by venous catheters or as routine thromboprophylaxis in patients receiving hormone or chemotherapy; similarly, thromboprophylaxis is not recommended as a means of increasing survival rates in patients with malignancies.[28]

Thromboprophylaxis should be initiated as soon as possible for patients with burns and additional risk factors for VTE (one or more of the following: advanced age, morbid obesity, extensive burns, particularly in lower extremities, concomitant lower extremity injuries, the use of femoral venous catheters and prolonged immobility). For travellers on long-haul flights for more than eight hours (even over 4-6 hours), the ACCP emphasizes the importance of general measures, such as maintaining adequate hydration, avoidance of tight clothing around the waist and lower extremities and exercising the lower-leg muscles. If these travelers have additional risk factors for VTE, they should also wear lower-leg elastic stockings that provide 15-30 mm Hg pressure at the level of ankle. Alternatively, they could be given a prophylactic dose of LMWH prior to the flight.[4, 29-31]

Thromboprophylaxis is recommended for pregnant women and those who gave birth in the last six weeks (without surgery). This is particularly important if they have one or more of the following risk factors presented in Table 4.

Table 4. Risk factors for VTE in pregnancy and puerperium.[4]

Reduced mobility for three days or more
Active malignancy or malignancy treatment
Age over 35 years
Obesity (BMI before pregnancy or in early pregnancy over 30 kg/m^2)
Admission to the intensive care unit
Dehydration, major blood loss or transfusion
Comorbidities (cardiac, metabolic, endocrine and respiratory diseases)
Acute infective diseases and inflammatory conditions
Positive family history of VTE in first-degree relatives
Ovarian hyperstimulation
Hyperemesis gravidarum, multiple pregnancy, preclampsia
Varicose veins with phlebitis
Known thrombophilia

Thromboprophylaxis is also advised for nonsurgical patients, *i*.e. those with acute medical illness, stroke, malignancy, central venous catheters or those who are confined to bed for longer than three days. Thromboprophylaxis is indicated for patients with stroke, especially for those with excluded hemorrhagic stroke or ruptured cranial and spinal vascular malformations. Despite the generally lower risk of hemorrhagic transformation of stroke or hemor-

rhage in other locations, mitigating factors such as reduced mobility, previous VTE, dehydration, presence of comorbidity like malignancy should influence the decision for prophylactic treatment.[4]

Because of the high incidence of arterial cardiovascular events in patients with previous spontaneous VTE antiplatelet agents should be considered as part of the regime for long-term secondary prevention of VTE.[13] In addition, to prevent VTE, other general, non-pharmacological measures can be used, such as weight reduction, prevention of dehydration, and mechanical means (elastic stockings, compression devices such as intermittent pneumatic compression or foot pumps). [14] Temporary anticoagulant therapy should be considered in a setting of inflammation, immobilization, estrogen therapy etc. A number of studies indicate that up to 40% of patients with previous VTE develop recurrent VTE. It should be noted that recurrent VTE occurs more frequently in those with spontaneous VTE than in patients with clearly defined risk factors.[14]

The decision to terminate anticoagulation therapy requires individual assessment of each patient, including their D-dimer values and ultrasound findings in lower limb veins. A balanced approach takes into account the risk of hemorrhage. [14] The choice of an anticoagulant regime must include assessment of the risk of venous thrombosis caused by heparin-induced thrombocytopenia type II while selecting an adequate non-heparin anticoagulant. [15-17, 28, 32-37]

Management of bleeding associated with oral anticoagulants

Because the use of any anticoagulant (old and new) may be complicated by the potential of bleeding, the clearance mechanisms, and the half-life of each of these agents one should understand in order to plan strategy for rapid reversal.[38] Options for reversing anticoagulation include: (1) withholding anticoagulation therapy (observation); (2) administering a specific reversal agent (e.g. oral or intravenous vitamin K if the bleed-related to a vitamin K antagonist); and (3) administering supplemental clotting-factor substitutes (e.g. fresh frozen plasma or prothrombin complex concentrates). However, appropriate supportive and symptomatic treatment is also needed (e.g. mechanical compression or surgical intervention).

Dabigatran and rivaroxaban have relatively short half-lives (dabigatran 12-17h, rivaroxaban 7-11h), in majority of patients with minor or mechanically controlled bleeding, observation and supportive care is the preferred strategy. In the event of a bleed or the need to take a patient emergently to surgery, there are pharmacodynamic parameters that can be measured to determine the approximate level of anticoagulation. For example, fordabig atran monitoring includes following: ecarin clotting time (ECT), thrombin time (TT) and activated partial thromboplastin time (aPTT), which, being relatively insensitive especially at high plasma concentrations, is not suitable for precise quantification of anticoagulant effect. Anticoagulation reversal agent for dabigatran is recombinant factor VIIa (rF-VIIa).

Epilogue

Anticoagulation is a common intervention in the prevention and treatment of thrombosis in multiple clinical settings. Its duration, both in primary and in secondary prevention, depends upon the risk for recurrent VTE as well as the risk for bleeding and present comorbidities.[7] Therefore, determining the length and type of an anticoagulant regimen must be guided by achieving the proper balance between the benefit of therapy and the risk of hemorrhage.[13] New oral anticoagulants (direct thrombin inhibitor and factor Xa inhibitors) may present simpler and safer treatment and prevention of VTE. Their immediate onset of anticoagulant effect, convenient administration, and lack of needed regular anticoagulation monitoring are of interest both for the patients and medical profesionals. Dabigatran is the first oral thrombin inhibitor approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more risk factors for stroke. Dabigatran has also been approved in several countries for the prevention of venous thrombosis in patients undergoing total knee or hip replacement. The RE-NOVATE study on the prevention of venous thromboembolism (VTE) after hip arthroplasty and RE-MODEL study on VTE prophylaxis after knee arthroplasty showed non-inferiority of dabigatran compared with enoxaparin adminstered in European doses of 40 mg daily, while the RE-MOBILISE study after hip arthroplasty confirmed dabigratan inferiority compared with enoxaparin at the North American dose of 30 mg twice daily. However, in the treatment and prevention of VTE, more data should be accumulated to show their ultimate place in therapy.

Author's contribution

The paper is designed and writen by its NMA. VK directed and supervised this project. IŽ and LjJ provided assistance in sourcing relevant literature and writing parts of the paper.

Conflict of interest

All authors declare no conflict of interest related to this paper.

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References

1. Fisher WD. Impact of venous thromboembolism on clinical managment and therapy after hip and knee arthroplasty. Can J Surg 2011;54:344-51.

2. Schulman S, Majeed A. A benefit-risk assessment of dabigatran in the prevention of venous thromboembolism in orthopaedic surgery. Drug Saf 2011;34:449-63.
3. Fareed J, Adiguzel C, Thethi I. Differentiation of parenteral anticoagulants in the prevention and treatment of venous thromboembolism. Thromb J 2011;9:5.
4. NICE Clinical Guidline 2010 (National Institute For Health and Clinical Exellence) London; www. nice.org.uk; 2010;1-50.
5. Hunt BJ. The prevention of hospital – acquired venous thromboembolism. Br J Haematol 2009; 144:642-52 .
6. Kaatz S, Qureshi W, Lavender RC. Venous thromboembolism: what to do after anticoagulation is started. Cleve Clin J Med 2011;78:609-18.
7. Kaatz S, Qureshi W, Fain C, Paje D. Duration of anticoagulation treatment in patients with venous thromboembolism. J Am Osteopath Assoc 2010;110:638-44.
8. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Blood Transfus 2011;9:120-38.
9. Goldhaber SZ. Risk factors for venous thromboembolism. JACC 2010;56:1-7.
10. Bauer KA. Duration of anticoagulation: applying the guidelines and beyond. Hematology Am Soc Hematol Educ Program. 2010:210-5.
11. East AT, Wakefield TW. What is the optimal duration of treatment for DVT? An update on evidence-based medicine of treatment for DVT. Semin Vasc Surg 2010;23:182-91.
12. Galanaud JP, Bosson JL, Quéré I. Risk factors and early outcomes of patients with symptomatic distal vs. proximal deep-vein thrombosis. Curr Opin Pulm Med. 2011;17:387-91.
13. Agnelli G, Becattini C. Treatment of DVT: how long is enough and how do you predict recurrence. J Thromb Thrombolysis 2008;25:37-44.
14. Prandoni P, Piovella C, Spiezia L, Dalla Valle F, Pesavento R. Optimal duration of anticoagulation in patients with venous thromboembolism. Indian J Med Res 2011;134:15-21.
15. Goldhaber SZ. Pulmonary embolism. In: Bonow RO, Mann DL, Zipes DP, Libby P, Braunwald E. Braunwald's Heart Disease. Ninth Edition. Philadelphia. Elsevier Saunders 2012;1679-95.
16. Hyers TM, Shetty HG, Campbell IA. What is the optimum duration of anticoagulation for the management of patients with idiopathic deep venous thrombosis and pulmonary embolism? J R Coll Physicians Edinb 2010;40:224-8.
17. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. Circulation 2010;121:1630-6.
18. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. Lancet 2010;376:2032–9.
19. Cristina L, Benilde C, Michela C, Mirella F, Giuliana G, Gualtiero P. High plasma levels of factor VIII and risk of recurrence of venous thromboembolism. Br J Haematol 2004;124:504-10.
20. Weltermann A, Eichinger S, Bialonczyk C, et al. The risk of recurrent venous thromboembolism among patients with high factor IX levels. J Thromb Haemost 2003;1:28-32.
21. Eischer L, Tscholl V, Heinze G, Traby L, Kyrle PA, Eichinger S. Hematocrit and the risk of recurrent venous thrombosis: a prospective cohort study. PLoS One.2012;7:e38705.
22. Eichinger S, Pecheniuk NM, Hron G, et al. High-density lipoprotein and the risk of recurrent venous thromboembolism. Circulation 2007;115:1609-14.
23. Hron G, Lombardi R, Eichinger S, Lecchi A, Kyrle PA, Cattaneo M. Low vitamin B6 levels and the risk of recurrent venous thromboembolism. Haematologica 2007;92:1250-3.
24. Gulesserian T, Hron G, Endler G, Eichinger S, Wagner O, Kyrle PA. Marburg I polymorphism of factor VII-activating protease and risk of recurrent venous thromboembolism. Thromb Haemost 2006;95:65-7.
25. Eichinger S, Hron G, Bialonczyk C, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. Arch Intern Med 2008;168:1678-83.
26. Pabinger I, Grafenhofer H, Kaider A, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis J Thromb Haemost 2005; 3: 949–54.
27. Daneschvar HL, Seddighzadeh A, Piazza G, Goldhaber SZ. Deep vein thrombosis in patients with chronic kidney disease. Thromb Haemost 2008;99:1035-9.
28. Geerts WH, Bergqvist D, Pineo GF, et al. American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(Suppl 6):381S-453S.
29. Schreijer AJM, Cannegieter SC, Meijers JCM, Middeldorp S, Büller HR, Rosendaal FR. Activation of coagulation system during air travel: a crossover study. Lancet 2006;367(9513):832-8.
30. Coppens M, Schreijer AJM, Berger FH, Cannegieter SC, Rosendaal FR, Büller HR. Mechanical prophylaxis for traveller's thrombosis: a comparison of three interventions that promote venous outflow. J Thromb Haemost 2007;5:1556-67.
31. Philbrick JT, Shumate R, Siadaty MS, Becker DM. Air travel and venous thromboembolism: a stematic review. J Gen Intern Med 2007;22:107-14.
32. Antonijevic N, Stanojevic M, Milosevic R, et al. Combined thrombophilic risk factors and essential thrombocythemia in patient with recurrent venous thromboembolic episodes-thirty-three-year follow-up. J Thromb Thrombolysis 2005;19:93-5.
33. Antonijevic NM, Milosevic R, Perunicic J, Stanojevic M, Calija B, Vasiljevic Z. Need for more intensive treatment of patients with acute pulmonary embolism caused by heparin- induced thrombocytopaenia Type II. Eur Heart J 2005;26:2745-6.
34. Antonijević N, Stanojević M, Peruničić J, et al. Thrombocytopenia induced by type II heparin and myocardial infarct: 2 case reports. Srp Arh Celok Lek 2004;132:33-7.
35. Antonijević N, Stanojević M, Milošević R, et al. Heparin-induced type II thrombocytopenia-new views on diagnosis and therapy. Med Pregl 2003;56:247-50.
36. Antonijević NM, Radovanović N, Obradović S, et al. Obstacles in the diagnostics and therapy of heparin-induced thrombocytopenia. Srp Arh Celok Lek 2010;138 Suppl 1:69-73.
37. Antonijević N, Kanjuh V, Zečević R, et al. Mogućnosti novih antitrombocitnih i antikoagulantnih lekova u okviru primarne perkutane koronarne intervencije. Balneoklimatologija 2011;35:101-19.

38. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etixilate- a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103: 1116-27.

39. Friedman R.J, Dahl O.E, Rosencher N. et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: A pooled analysis of three trials. Thromb Res.2010;126:175–182.

Faktori rizika za venski tromboembolizam i trajanje antikoagulantne terapije

Nebojša M. Antonijević, Vladimir Kanjuh, Ivana Živković, Ljubica Jovanović

APSTRAKT

Utvrđivanje reverzibilnih i ireverzibilnih faktora rizika za venski tromboembolizam (VTE), preduslov je za određivanje adekvatnog režima tromboprofilakse. Podaci ukazuju da najveći procenat plućnih embolija nastaje u nehirurških bolesnika. U hirurških bolesnika VTE se u velikom broju javlja posle otpusta iz bolnice. Ova saznanja nameću potrebu za adekvatnom zaštitom od VTE obolelih od inflamatornih oboljenja, akutnih bolesti i drugih nehirurških oboljenja, kao i optimalizacijom antikoagulantnog režima posle hirurških intervencija. Utvrđivanje faktora rizika za VTE, određivanje prisustva stečene i urođene trombofilije, okultnog ili do tada neprepoznatog maligniteta pomoći će definisanju antikoagulantnog režima u hirurških i nehirurških bolesnika u sekundarnoj prevenciji VTE. Praćenje vrednosti D-dimera, ultrazvučna procena rezidualne venske tromboze, ehokardiografski parametri uz druge relevantne kliničke podatke ukazuju na rizik od nastanka rekurentnog VTE. Ove procedure omogućavaju utvrđivanje optimalne dužine antikoagulante terapije u svakog bolesnika ponaosob, sa posebnom pažnjom na prisutne komorbiditete i hemoragijsku tendenciju.

KLJUČNE REČI

Venski tromboembolizam, tromboprofilaksa, rekurentna tromboza, rizik od krvarenja.

CONTINUING MEDICAL EDUCATION

Questions and Answers

Ова рубрика (Q & A) садржи незнатно измењене сегменте из наведене литературе или за ову прилику написан текст. Циљ нам је да ови прилози послуже читаоцу као вежба за унапређење стручног енглеског језика.

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

Scripta Medica

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Milka Mavija

Department of Ophthalmology, University Medical Center Banja Luka, 78000 Banja Luka

Sanja Ilić

Department of Endodontics, Institute of Dentistry, 78000 Banja Luka

Verica Pavlić

Department of Periodontology, Institute of Dentistry, 78000 Banja Luka

Correspondence

Verica Pavlić, DDS, Ph.D.
Department of Periodontology
Institute of Dentistry
78000 Banja Luka

Questions

1. What is the role of the cranial nerves in activities associated with vision and in the act of speaking?

2. What are the main characteristics of central retinal artery occlusion?

3. Describe the Purkinje Effect.

4. How did daltonism get its name?

5. The posterior portion of the eye is vascularized by three circulations (retinal, choroid, and optic nerve). How are each of these affected by hypertension?

6. Which are the key points for assessing ocular trauma?

7. How are specimens collected for microbiological analysis of eye infections?

8. Describe the etiology and diagnosis of left ventricular hypertrophy.

9. Define the term "genomics."

10. Is there a significant genetic component affecting blood pressure and hypertension?

11. Arterial hypertension has a relatively low prevalence in children compared to adults. At what age should one begin to monitor blood pressure yearly in children?

12. A 16-year-old girl is brought to a physician by her mother, who states that her daughter has been steadily losing weight. The adolescent denies there is a problem and states that she is in no way underweight. The physician determines that the girl is 5 ft 6 in tall and weights 90 lb. Which of the following laboratory tests is most helpful in assessing the severity of starvation in this patient?
A. Complete blood count and differential white blood cell count
B. Thyroid function studies
C. Serum potassium level
D. Determination of albumin in blood
E. Liver function studies

13. The adolescent described above is diagnosed with anorexia. After stabilization of her nutritional status on a specialized inpatient unit, she is discharged home, with plans for follow-up therapy as an outpatient. Which of the following treatments have been shown to be effective in treating anorexia nervosa as an outpatient?
A. Psychodynamic psychotherapy
B. Family therapy
C. Brief supportive therapy
D. Group therapy
E. Insight-oriented psychotherapy

14. A 46-year-old woman with stage III ovarian cancer presents to your outpatient clinic with nausea. The nausea has worsened over the past 2 days, and she is unable to consume anything beyond her medications and a few sips of water without vomiting. She is receiving chemotherapy with carboplatin and paclitaxel and notes that she has not had difficulty with nausea during or after chemotherapy because her oncologist administers antiemetics prophylactically before each session. It has been 17 days since her last chemotherapy. The nausea does not seem to occur with movement; it is worse after eating solids and liquids and is accompanied by abdominal distension. She has minimal abdominal pain, which is managed with oxycodone, 10 mg orally 3 times a day. Her last bowel movement was 4 days ago. Abdominal radiography (obstruction series) shows no air-fluid

levels, no free air, and no evidence of obstruction, but there is a moderate amount of stool in the colon.

Which one of the following is the most appropriate antiemetic to prescribe initially to this patient?
A. Metoclopramide, 10 mg orally 4 times a day
B. Ondansetron, 8 mg orally twice a day
C. Promethasine, 25 mg orally (or suppository) every 6 hours
D. Lorazepam, 1 mg orally every 6 hours
E. Granisetron, 1 mg orally once daily

15. Name the hearing loss due to the aging processes.

16. Will a diet high in fructose, cholesterol, and saturated fats produce fibrosis of the liver?

17. What is the meaning of *editorial style*?

18. Water is ubiquitous in biology and in many other areas of nature. However, generally, water in tissues is not in the form of bulk liquid. Water in cells interacts with cell membranes, the surfaces of proteins, the interiors of proteins, and many other biological molecular species. Water plays a fundamental role in many diverse processes because it can undergo structural reorganization.

Are the dynamics of water very fast or slow?

19. Because reproduction is arguably the most important event in any animal's life, understanding how reproduction is regulated offers important insights into the evolution of a particular species. Learning how social and physiological factors collaborate to control reproductive activity is essential for understanding the selective pressures that shape reproductive control.

How does reception of social information reach brain regions responsible for initiating reproductive behaviors? How are gamete (sperm, oocyte) production and steroid hormone release controlled? Ultimately, how do social interactions influence gene expression to control reproduction?

20. What is the main dental concern for patients treated with the newer drugs for management of osteoporosis and malignant bone pathology?

21. Which serum biomarker may be used to indicate the risk of bisphosphonate-related osteonecrosis of the jaw?

22. What are the newest approaches in treatment of xerostomia?

23. Why do teeth change their color?

24. Which access has better outcome in ST-segment elevation acute coronary syndrome undrergoing early invasive treatment: radial or femoral?

25. Can overweight as defined by body mass index (BMI) actually have a protective association with mortality?

Answers

1. *Cranial nerve activities associated with vision*. Stimulation of the eye produces not only conscious visual sensations but also ancillary responses that utilize many peripheral nerves. The constriction of pupils to bright light and the focusing of the lens are effected via the parasympathetic fibers of the oculomotor nerve, whereas dilatation of the pupil in dim light is mediated via sympathetic fibers from the upper thoracic spinal cord levels. Pain from irritation of the cornea is transmitted by the trigeminal nerve. Blinking of the eyelid results from stimulation by the facial nerve; movements of the eye and raising the eyelid follow stimulation by the oculomotor, trochlear, and abducens nerves; the secretion of tears from the lacrimal gland results from stimulation of parasympathetic fibers of the facial nerve.

Act of speaking. Contraction and relaxation of the thoracic and abdominal musculature during exhalation and inhalation, mediated by spinal nerves, are essential preliminaries to the act of speaking. Vowels are formed by the vibration of the vocal cords of the larynx, which are innervated by the vagus nerve; resonance is aided by relaxation of the pharynx and palatine arch muscles (this is especially pronounced in singers), which are innervated by the glossopharingeal and vagal nerves. Certain consonants, such as Ts and Ds, are formed by the action of the tongue, which is innervated by the hypoglossal nerve; others, such as Ss and Cs, are formed by the combined action of the jaw, tongue, and lips, involving the trigeminal, hypoglossal, and facial nerves. The lips alone form the consonant P through activation of the facial nerve.

2. *Sudden, severe, and painless loss of vision in one eye is characteristic of central retinal artery occlusion (CRAO).* The retina becomes opaque and edematous, particularly in the posterior pole where the nerve fibers and ganglion cell layers are thickest. The orange reflex from the intact choroidal vasculature beneath the foveola stands out in contrast to the surrounding opaque neural retina, producing the characteristic cherry- red spot.

The central retinal artery reopens or re-canalizes with time, and the retinal edema clears. However, the retinal arterial infarction generally has a devastating effect on visual acuity. In one study, 66% of CRAO eyes studied had final vision worse than 20/400, and 18% had vision of 20/40 or better. Most cases of 20/40 or better vision had a patent cilioretinal artery, which preserves the central macula. Loss of vision to the level of no light perception at all is often associated with choroidal vascular insufficiency (ophthalmic artery occlusion) in addition to occlusion of the central retinal artery.

3. *Purkinje Effect*. The Purkinje effect (sometimes called the Purkinje shift, or dark 2. adaptation) was named after the Czech anatomist, Jan Evangelista Purkyně, who noted that

light blue flowers appear bluer at dawn or twilight than at midday. At dusk, red flowers appear black.

The effect occurs because color-sensitive cones in the retina are the most sensitive to yellow light, whereas the rods, which are more light sensitive (and thus more important in low light) respond best to green-blue light, even though they do not distinguish colors. This is why humans become virtually color-blind under low levels of illumination, for instance in moonlight.

The insensitivity of rods to long-wavelength light enables us to use red lights under certain circumstances, as in the control rooms of submarines, in research laboratories, or during naked-eye astronomy. Submarines are dimly lit to preserve the night vision of the crewmembers working there, but the control room must be sufficiently lit for reading of instrument panels. Under red light, or with red goggles, the retinal cones receive enough light to provide photopic vision (namely the high-acuity vision required for reading). Because the rods are not saturated by bright light and are insensitive to long-wavelength red light, the individual can remain dark adapted, in case he needs to use the periscope at night, for example.

Red lights are also often used in research settings. Many research animals, such as rats and mice, have limited photopic vision, because they have far fewer cone photoreceptors. Red lights keep the animals "in the dark" (the active period for nocturnal animals), while allowing the human researchers, who have one kind of cone that is sensitive to long wavelengths, to read instruments or perform procedures that would be impractical even with fully dark adapted (but low acuity) scotopic vision. For the same reason, zoo displays of nocturnal animals often are illuminated with red light.

The Purkyně effect was discovered in 1819 by Jan Evangelista Purkyně, a polymath (knowledgeable man) who would often meditate at dawn during long walks in the blossoming Bohemian fields. Purkinje noticed that his favorite flowers appeared bright red on a sunny afternoon, while at dawn they looked very dark. He reasoned that the eye has not one but two systems adapted to see colors: one for bright overall light intensity and the other for dusk and dawn.

Purkinje wrote in his *Neue Beiträge* (translated from the German)*:*

Objectively, the degree of illumination has a great influence on the intensity of color quality. In order to prove this most vividly, take some colors before daybreak, when it begins slowly to get lighter. Initially one sees only black and grey. Particularly the brightest colors, red and green, appear darkest. Yellow cannot be distinguished from a rosy red. Blue became noticeable to me first. Nuances of red, which otherwise burn brightest in daylight, namely carmine, cinnabar and orange, show themselves as darkest for quite a while, in contrast to their average brightness. Green appears more bluish to me, and its yellow tint develops with increasing daylight only.

4. An article entitled "Deficiency of color vision" was published in 1798 by the English chemist, John Dalton. He described his own color blindness. Because of Dalton's work, the general condition has been called *daltonism*, although this term in English now applies more narrowly to deuteranopia alone.

Colorblindness, or color deficiency, is a sex-linked characteristic found to some degree in 8 % of males and 1.5 % of females. There is no actual blindness but a deficiency of color vision. The most usual cause is a fault in the development of one or more sets of retinal cones that react to various wavelengths in light and transmit that information to the optic nerve. This type of color blindness is usually a sex-linked condition. The genes that produce photo-pigments are carried on the X chromosome. If some of these genes are missing or damaged, color blindness will be expressed in males with a higher probability than in females because males lack a second X chromosome. A functional gene on only one of the two X chromosomes in the female supplies the needed photo-pigments. Color blindness can also result from physical or chemical damage to the eye, the optic nerve, or parts of the brain. For example, people with achromatopsia suffer from a completely different disorder, but are nevertheless unable to see colors.

All classifications of colorblindness are based on subjective defects in perception, even though the specific cause is unknown. Individuals with three-color vision (trichromats) are those with 1) normal vision, 2) weak red vision (protanomaly), or 3) weak green vision (deuteranomaly). Individuals with two-color vision (dichromats) are those who who 1) cannot perceive red (protanopia), 2) cannot perceive green (deuteranopia) or 3) cannot perceive blue (tritanopia). Persons with tritanopia are rare, as are those with no color vision (monochromatomats). Monochromatomas see the environment in shades of light and dark, and some of them experience pain during light stimulation.

Color blindness is usually classed as a mild disability, but there are occasional circumstances where it appears advantageous. Some studies conclude that colorblind people are better at penetrating certain color camouflages. This might indicate an evolutionary advantage to account for the high prevalence of red–green color blindness.

5. The retina is the only tissue in the body in which blood vessels can be observed directly. Examination of the ocular fundi enables the physician to observe the effects of hypertension in a unique vascular bed. The three circulations of the posterior portion of the eye derive from branches of the ophthalmic artery. The retinal circulation is particularly sensitive to local tissue metabolic needs (glucose consumption and oxygen use are 3-fold higher than in any other tis-

sue in the body) and is susceptible to damage from circulatory dysfunction.

Retinal circulation. Changes in retinal blood vessels are the most common vascular lesions in the eye due to systemic hypertension. Hypertensive retinopathies have been classified by a number of investigators (*e.g.*, Keith, Wagner, and Baker, 1939, and those of Scheie, 1953), but these classifications are less useful clinically than a careful description of the extent of lesions in the eye. Hypertensive retinopathy may include various combinations of lesions. Some are relatively specific for hypertensive retinopathy, *e.g.*, "copper wiring" of arterioles, "arteriovenous nicking" and related crossing changes, as well as arterial macroaneurysms. Additional "hypertensive" lesions found in other disorders include the "cotton-wool spots" in diabetic retinopathy, systemic lupus erythematosus, retinal vein occlusions, and acquired immune deficiency syndrome. Flame-shaped intraretinal hemorrhages also occur in diabetic retinopathy, profound anemia, the leukemias and other blood dyscrasias. Arterial "silver wiring" may occur in diabetic retinopathy, collagevascular diseases, and arterial occlusive diseases.

Chorioidal circulation. Hypertensive changes in the chorioidal vessels occur much less frequently than hypertensive changes in the retina. Hypertensive chroidopathy occurs because the short choroidal arteries feed at right angles into the choroidal capillaries, allowing direct transmission of systemic blood pressure to the capillaries. Initial changes may include focal regions of choriocapillary nonperfusion resulting from fibrinoid necrosis of the vessels. These defects are recognized only by the use of specific techniques such as intravenous fluorescein angiography. The retinal pigment epithelium over these nonperfused regions may subsequently develop a yellowish coloration called the Elschnig spot. This eventually becomes a scar with a pigmented center and an atrophic surrounding halo.

Optic nerve circulation. Hypertensive changes in the optic nerve are relatively uncommon. The principal optic nerve lesion of hypertension is disc edema.

6. Key points for managing ocular trauma include following:

-Take an accurate history.
-Search for foreign bodies under the upper lid.
-Suspect a subtarsal foreign body with persistent pain in an intact eye.
-Irrigate chemical injuries immediately with clean water.
-Suspect a perforating eye injury if the pupil is not round, a cataract develops rapidly or vitreous hemorrhage is present.

7. Several types of specimens may be collected for the microbiological analysis of the eye infections. These include conjunctival scrapings obtained with a swab or sterile spatula for the diagnosis of conjunctivitis, corneal scrapings collected with a sterile spatula for the diagnosis of keratitis, vitreous fluid collected by aspiration for the diagnosis of endophtalmitis, and fluid material collected by aspiration from a tissue biopsy for the diagnosis of periorbital cellulitis.

Direct inoculation of agar culture plates and preparation of smears in the clinic or at the bedside is recommended for the small volumes of specimens collected from corneal scrapings and vitreous fluid. A close working association between the laboratory and ophthalmologist will ensure a supply of appropriate culture media, correct techniques for inoculation media, and rapid transport of plates and smears to the laboratory.

8. Left ventricular hypertrophy (LVH) is the response of the heart to chronic pressure, volume overload, or both. The most common causes of cardiac hypertrophy are hypertension and valvular heart disease. Genetic factors determine the extent of the hypertrophic response to existing stimuli, and several mutations have been identified in kindreds with severe familial forms of LVD. These can occur even in the absence of hypertension.

The diagnosis of LVH an be made in several ways, but it is commonly identified by electrocardiogram (ECG) on the basis of increased voltage and repolarization abnormalities, or by an echocardiogram that calculates left ventricular mass (LVM) from measured LV wall thickness and internal chamber dimensions.

9. The totality of DNA possessed by an individual constitutes his or her genome. Genomics, as distinct from genetics, is the study of the organization and evolutionary history of DNA. The total human genome is approximately three billion bases long; this is the product of two parental genomes of three billion base pairs each (*i.e.,* roughly six billion "bits" of information divided into pairs).

10. There is evidence for a significant genetic component of blood pressure in humans, and several intermediate phenotypes closely associated with hypertension relate directly to specific genes. Intermediate phenotypes are quantifiable biologic traits (such as angiotensinogen levels or salt sensitivity) that, in appropriate combinations, account for a fraction of the overall risk for the development of hypertension.

Numerous linkage analyses using 300 to 500 markers spread over all chromosomes suggest several locations for hypertension genes. Some of the more consistent areas are on chromosome arms 1q, 2p, 2q, 8p, 17q, and 18q. Other less consistent regions may still harbor important genes. Genes involving the renin-angiotensin system have been the ones most systematically studied.

A family history of hypertension is commonly used as a measure of familial aggregation, and it can be a surrogate measure for undefined risk factors shared by the family. Controlling or removing behavioral risk factors confers the

greatest benefit for individuals with the greatest genetic risk. Interactions between genetic variations and environmental factors such as stress, diet, and physical activity also contribute to the development of essential hypertension.

It is well known that hypertensive individuals exhibit a varied response to antihypertensive drugs, likely reflecting a wide variety of factors, including differences in pharmacodynamic and pharmacokinetic traits. Pharmacogenetics, the study of genetic variations that influence responses to pharmacogenetic agents, is an emerging field based upon genetic-environmental interactions.

11. Measurement of blood pressure in children is recommended yearly after the age of three years. The diagnosis of hypertension in children now uses the fifth Korotkoff sound to define diastolic blood pressure. It also depends on height.

The average systolic BP at one day of age is approximately 70 mm Hg in full-term infants, and it increases to approximately 85 mm Hg by one month of age. During the first year of life, BP increases at a greater rate in premature infants than in full-term infants. BP then increases steadily throughout the first two decades of life. Greater weight, greater height, and family history of hypertension are known to be associated with higher levels of BP in children and adolescents.

12. The correct answer is D. Determination of the albumin level can help assess the current extent of starvation in a patient. It is an important index in the treatment of anorexic patients.

13. The correct answer is B. Family therapy, both short-term and long-term, has been shown to improve outcomes in adolescent patients with anorexia nervosa. Many of these family treatments are completed in stages, generally beginning with developing parental control over the eating and gradually turning control over to the adolescent as nutritional status improves. Some cognitive behavioral therapies may be effective, but there is little evidence for the others listed.

14. The correct answer is A.

Comment: This patient's nausea is likely due to gastrointestinal distension and irritation from both constipation and her ovarian cancer; there is possibly a direct effect from the opioid therapy as well. Opioid–induced nausea is primarily mediated by dopamine. In this case, serotonin receptors in the gastrointestinal tract, serosa, and viscera are also involved. Dopamine blockade would likely be helpful for this patient. Metoclopramide, a dopamine D2 receptor antagonist with some peripheral serotonin antagonism, would be the best choice. Prochlorperazine and haloperidol would also be reasonable choices.

Enough time has passed since the patient's most recent chemotherapy that it should not be a major contributor to her nausea at this time. Importantly, she does not appear to have a bowel obstruction. It is important to rule out obstruction to preclude the need for surgical intervention or nasogastric tube placement. Obstruction should also be ruled out before administering metoclopramide, given the promotility actions of the drug. Anxiety does not seem to be a major component of the patient's condition, and lorazepam alone has poor antiemetic effects.

Toxin-induced nausea, such as medication effects and electrolyte disturbances (*e.g.,* hypercalcemia) are mediated through the chemoreceptor trigger zone (CTZ), within the area postrema in the floor of the fourth ventricle. Serotonin and dopamine are the two most active neurotransmitters in the CTZ. Serotonin antagonists, such as haloperidol, metoclopramide, or prochlorperazine, are most effective for treatment of CTZ-mediated nausea. Promethazine is a weak antagonist of dopamine, and it generally acts by inducing sedation via antihistaminic and anticholinergic pathways. Promethazine is not routinely recommended for nausea, given its limited efficacy and wide range of adverse effects.

Conclusion: Selection of an antiemetic should consider the mechanism of the drug's action and the putative factors that contribute to the nausea.

15. The term presbycusis refers to the hearing loss due to aging. Aging generally affects the cochlea, but it may also affect the central auditory pathway. The deafness of aging is characteristically bilaterally symmetrical and predominantly affects high tones. The basal turn of the cochlea is involved in perception of high tones, while lower turns are appreciated higher up in the cochlear spiral. Because it is nearest the oval window through which vibrations enter the cochlea, the basal turn bears the brunt of 'wear and tear' and hearing for high tones fails first.

In aged individuals, the ear has likely been exposed to one or more other causes of hearing loss. Presbycusis appears to begin earlier in urban than in rural communities.

Pathological changes can affect any of these four sites in the cochlea:
a. In 'sensory presbycusis' the organ of Corty in the basal turn of the cochlea atrophies, with disappearance of hair cells.
b. 'Strial presbycusis' exhibits patchy atrophy of the stria vascularis, with cystic changes.
c. In 'cochlear conductive prebycusis' the basal membrane becomes stiffened and calcified, especially in the basal turn.
d. 'Neural presbycusis' involves atrophy of the spiral ganglion with severe loss of ganglion cells.

Audiograms reveal that neural presbycusis is associated with severe loss of speech discrimination, and strial prebycusis shows a fairly even hearing loss at all frequencies with good speech discrimination. High tone loss is charac-

teristic of the sensory and cochlear conductive forms.

16. A diet high in cholesterol, saturated fats and fructose (*i.e.,* "fast food") promotes development of nonalcoholic fatty liver disease (NAFLD), insulin resistance, and metabolic syndrome. The progressive form of NAFLD, nonalcoholic steatohepatitis (NASH), is characterized by inflammation and fat accumulation in the liver, which can lead to cirrhosis and ultimately to loss of liver function.

A newly developed animal model of NASH shows gene expression typical of metabolic syndrome and NASH with progressive fibrosis. It is interesting to note that the observed effects were more pronounced in male mice than in females.

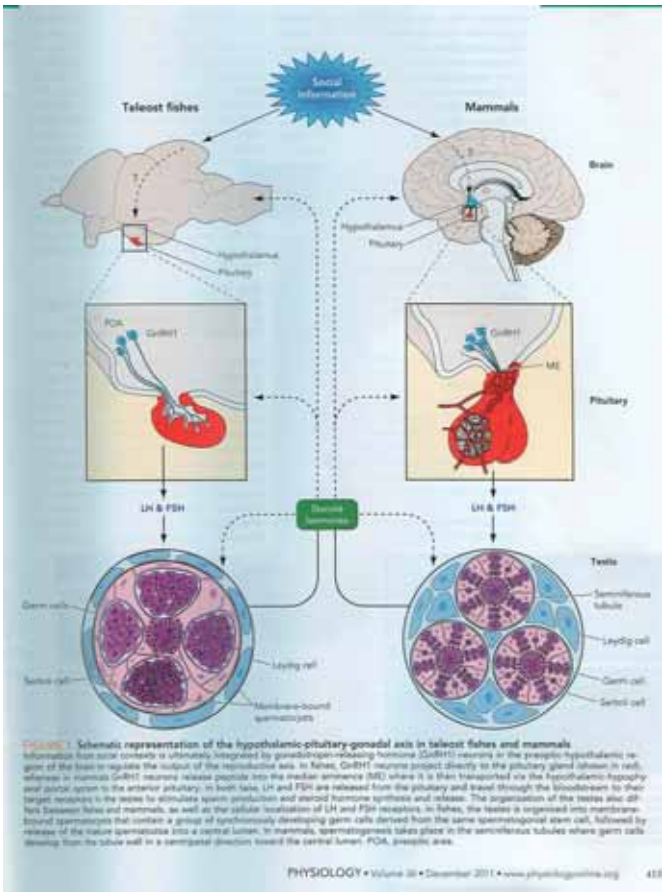
17. When editors or typesetters refer to *style*, they do not mean writing style, but rather editorial style—the rules or guidelines a publisher follows to ensure clear, consistent presentation of the printed word. Editorial style concerns uniform use of punctuation and abbreviations, construction of tables, section of headings, and citation of references, as well as many other elements that are part of every manuscript.

An author writing for a particular publication must follow the style rules established by the publisher to avoid inconsistencies among journal articles or book chapters. For example, without rules of style, three different manuscripts might use *sub-test*, *subtest*, and *Subtes*t or *E-mail, e-mail* or *email*. Although the meaning of these two words in three variations is the same, and the choice of one style over the other may seem arbitrary (*subtest* and *e-mail* are APA style), such variations in style may distract or confuse the reader.

18. The dynamics of water are very fast, picosecond to tens of picosecond on the time scale. Ultrafast infrared (IR) experiments performed on the hydroxyl (OH) stretch of water can be used to measure the dynamics of water molecules under thermal equilibrium conditions.

Water at an interface behaves differently in a system where the characteristic nanodimension is relatively large (>10 nm) vs. one in which it is small (<4 nm). Water dynamics depend on the nature of the large molecular structures the water is interacting with, but also to an even greater extent on the size of the nanoscopic water system.[1*]

19. Reproduction in all vertebrates is controlled by the hypothalamic-pituitary-gonadal axis. In many species the social environment influences this axis, and consequently reproductive fitness. Numerous studies in vertebrates demonstrate activation of reproduction by olfactory, auditory, tactile, and visual social signals; these signals can reflect changes in the number, size or axonal densities of gonadotropin-releasing hormone 1(GnRH1) peptide, either delivered directly via neuronal projections in fishes or via the hypothalamic-pituitary portal system in tetrapods. The peptide binds to GnRH receptors on these secondary cells to induce synthesis and release of two gonadotropin hormones, LH and FSH, which then target the gonads (testes or ovaries) to stimulate steroid production and gamete development. Social behaviors are defined as interactions among members of the same species that influence immediate or future behaviors, including production, reception, and interpretation of communicative signals in a context-dependent manner.



This Figure is from an article entitled Social Regulation of Gene Expression in the Hypothalamic-Pituitary-Gonadal Axis by Karen P. Maruska and Russell D. Fernald in *Physiology* (2011;26:412-23). Reproduced by permission of The American Physiological Society.

20. Recently introduced medications such as bisphosphonates (alendronate, etidronate, clodronate, pamidronate, risedronate, zoledronate, etc.) are used in the therapy of osteoporosis, Paget's disease and the hypercalcemia of malignancy. These new agents broaden the range of current treatment options. Even though contemporary studies suggest positive effects of bisphosphonates used in everyday practice, there are also risks associated with their use, such as inhibition of osteoclast functions that lead to inhibition of normal bone turnover. This can result in impaired wound

[1] **We refer to water confined on nanometer length scales as "nanoscopic water."*

healing following trauma (such as dental surgery) or even spontaneous non-healing bone exposure. Because bisphosphonates are preferentially deposited in bone with high turnover rates, the levels of bisphosphonates within jawbones may be elevated selectively. The main dental concern is bisphosphonate-related osteonecrosis of the jaw. Numerous studies indicate a relation between use of bisphosphonates and osteonecrosis after dental extraction. Patients who are taking intravenous bisphosphonates for cancer and must undergo dental extraction have an incidence of osteonecrosis of the jaw of one in 10-15 patients, or 10-15 % of this population.

To date the incidence of jaw osteonecrosis in patients treated with intravenous zoledronic acid and subcutaneous denosumab for osteoporosis is unknown, but it is assumed to be low. Since these substances can be considered as drugs, patients should have their oral health checked before treatment. Their bone turnover will be markedly suppressed post-infusion, and dental extractions must be avoided for at least several months.

However, strontium ranelate or teriparatide pose no risks for osteonecrosis of the jaw. These agents have completely different mechanisms of action than the bisphosphonates. In fact, teriparatide may be a good treatment option for bisphosphonate-related osteonecrosis of the jaw.

21. C-terminal telopeptide (carboxy-terminal collagen crosslinks, also known as CTX) is a serum biomarker for bone turnover. It can be useful in assessing risk and guiding clinical evaluation of the nonsurgical treatment response as well as a guide for timing of surgery to pose the least risk of complications during healing. All patients with bisphosphonate-related osteonecrosis of the jaw were found to have low bone turnover as measured by C-terminal telopeptide at the time of onset. The morning fasting CTX test results cannot predict exactly who will develop bisphosphonate-related osteonecrosis of the jaw. CTX values are useful for stratification of relative risk: less than 100 pg/mL indicates high risk; between 100 pg/mL and 150 pg/mL indicates moderate risk; above 150 pg/mL indicates minimal risk.

22. Xerostomia is subjective complaint of mouth/oral dryness, caused by a reduction in normal salivary secretion due to different causes. Even though there are many treatment modalities available to enhance salivary flow, the therapy often remains unsatisfactory. Unknown etiology and lack of specific therapy make management of this disease very difficult. Low-level laser therapy (LLLT; low-level laser irradiation, photo-bio-modulation) has been used extensively as a non-invasive tool for reduction of xerostomia. LLLT significantly enhances salivary secretion and improves antimicrobial characteristics of secreted saliva (increased levels of secretory immunoglobulin A, sIgA). Furthermore, LLLT improves salivary flow and regeneration of salivary duct epithelial cells. It can be safely and effectively used as an advanced treatment modality for reduction of xerostomia.

23. The causes of color changes in vital teeth are: secondary mineralization after trauma, enamel defects, use of systemic drugs such as fluoride, tetracyclines (tetracycline, oxytetracycline, doxycycline, minocycline)[2*], ciprofloxacin, amoxicillin, hemorrhage (after vital extirpation), and exposure to coffee, red wine, tobacco, certain spices, etc. The main causes of the changes in color for nonvital teeth are: pulp necrosis, endodontal drugs and treatment materials such as iodoform, endometasone, and restorative materials, such as amalgam.

24. In patients with acute coronary syndrome (ACS), major bleeding is a significant predictor of worse outcome. Access site complications represent a significant source of bleeding for those patients undergoing revacularization, especilly when femoral access is used. Observational data and small randomized trials suggest that radial instead of femoral access for coronary angiography/intervention results in fewer bleeding complications, with preserved and possibly improved efficacy, further translating into mortality benefit in higher-risk patients, such as those with ST-segment elevation myocardial infarction (STEMI).

In the two large randomized trials: Radial Versus Femoral Access for Coronary Intervention (RIVAL) and Radial Versus Femoral Investigation in ST Elevation Acute Coronary Syndrome (RIFLE-STEACS) investigators report a detailed analysis the radial and femoral approaches in patients with STEMI. The RIVAL trial was performed in 32 countries (7.021 patients), and RIFLE-STEACS trial was performed at 4 Italian centers.

In patients with STEMI, radial artery access reduced the primary outcome and mortality. No such benefit was observed in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS). The radial approach may be preferred in STEMI patients, provided adequate operator and center expertise is present

25. Overweight-obesity is defined as a BMI of 27.8 or greater for men and 27.3 or greater for women. The WHO defined preobesity (overweight) as a BMI of 25 or greater and class (grade) 1 obesity as a BMI of 30 or greater, class 2 as a BMI of 35 or greater, and class 3 as a BMI of 40 or greater. Using a sample of more than 2.88 million individuals with more than 270 000 deaths, it was found (Flegal KM, et al. *JAMA* 2012;309:71-82) that all-cause mortality hazard ratios (HRs) relative to normal weight (defined as a BMI of 18.5-<25) for overall obesity (grades 1, 2, and 3 combined; HR, 1.18 [95% CI, 1.12-1.25]). Higher all-cause mortality was not observed in individuals with grade 1 obesity. Mortality was significantly lower among those who were overweight individuals.

Body mass index accounts for about two-thirds of the be-

[2] **Tetracyclines stain developing teeth, even when taken by the mother during pregnancy. These drugs discolor permanent teeth (yellow-gray-brown), from infancy and childhood to eight years old.*

tween-individual variation in total adiposity. Body mass index not account for sex, race, age, and fitness differences in fat mass even at the same body weight. Body mass index is known to be an imperfect predictor of metabolic risk. Some individuals with normal BMI have an overweight-obesity metabolic pattern. Factors such as cardiorespiratory fitness are also independent predictors of total mortality in some groups after controlling for BMI, waist circumference, and percentage of body fat. Newer markers such as those representing systemic inflammation may also extend risk prediction beyond BMI. Establishing BMI is only the first step toward a more comprehensive risk evaluation.

Literature

Anonymous. *Publication manual of the American psychological association,* fifth edition. Washington, DC, American Psychological Association, 2001.

Antonini LG, Luder HU. Discoloration of teeth from tetracyclines-even today? *Schweiz Monaatssehr Zahnmed* 2011; 121:414-22.

Charlton M, Krishnan A, Viker K, et al. The fast food diet mouse: a novel small animal model of NASH with high histologic and physiologic fidelity to the human condition. *Am J Physiol Gastrointest Liver Physiol,* doi:10.1152/ajpgi.00145.2011

Fayer MD. Water in a crowd. *Physiology* 2011;26:381-92.

Heymsfield SB, Cefalu WT. Does body mass index adequately convey a patient's mortality risk? JAMA 2013;309:87-8.

Hickish G W. *Ear, nose and throat disorders*. Edinburgh, Churchill, 1985.

Izzo JL, Black HR, eds. *Hypertension primer*, third edition. Dallas, American Heart Association, 2003.

James B, Chew C, Bron A. *Lecture notes on ophthalmology*, eight edition. Oxford, Blackwell, 1997.

Jolly SS, Niemelä K, Xavier D, et al. Design and rationale of the radial versus femoral access for coronary intervention (RIVAL) trial: a randomized comparison of radial versus femoral access for coronary angiography or intervention in patients with acute coronary syndromes. *Am Heart J* 2011;161:254-60.

Kažić T. *Gotovi lekovi. Priručnik za farmakoterapiju,* deveto izdanje. Beograd, Integra, 2003.

Maruska KP, Fernald RD. Social regulation of gene expression in the hypothalamic-pituitary-gonadal axis. *Physiology* 2011;26:412-23.

Marx RE, Cillo JE Jr, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 2007;65:2397-410.

McCullough M. New drugs for osteoporosis. *Australian Prescriber* 2011;34:181.

McCullough M, Goss A. Bone turnover markers. *Australian Prescriber* 2012;35:159.

Mehta SR, Jolly SS, Carins J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol* 2012;60:2490-9.

Pavlić V. The effects of low-level laser therapy on xerostomia (mouth dryness). *Med Pregl* 2012;65:247-50.

Regillo CD. *Retina and vitreous. Basic and clinical science course*. San Francisco, American Academy of Ophthalmology, 2008.

Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2012;60:2481-9.

Swetz KM, Carey EC, Bundrick JB. Clinical pearls in palliative medicine 2012. *Mayo Clin Proc* 2012;87:1118-23.

Toy E, Klamen, D. *Case files: Psychiatry,* fourth edition. New York, Lange, 2012.

Versalovic J, ed. *Manual of clinical microbiology*, tenth edition. Washington, DC, ASM Press, 2011.

Публикације аутора из Републике Српске у часописима уврштеним у *Medline* базу података

Quality of life in patients with multiple sclerosis in Republic of Srpska.
Tadić D, Dajić V.
Med Glas (Zenica). 2013 Feb;10(1):113-9.

Influence of the Green Tea Leaf Extract on Neurotoxicity of Aluminium Chloride in Rats.
Jelenković A, Jovanović MD, Stevanović I, Petronijević N, Bokonjić D, Zivković J, Igić R.
Phytother Res. 2013 Mar 11. doi: 10.1002/ptr.4962. [Epub ahead of print]

Evaluation of set-up errors in head and neck radiotherapy using electronic portal imaging.
Strbac B, Jokic VS.
Phys Med. 2013 Jan 2. doi:pii: S1120-1797(12)00208-6. 10.1016/j.ejmp.2012.12.001. [Epub ahead of print]

The analysis of limbs acute ischemia during seasons on the territory of South Serbia.
Damnjanović Z, Jovanović M, Janković I, Cvetanović V, Smiljković I, Janković D.
Med Glas (Zenica). 2013 Feb;10(1):161-3.

Influence of age and length of service on the level of stress and burnout syndrome.
Stanetić K, Tesanović G.
Med Pregl. 2013 Mar-Apr;66(3-4):153-62.

Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions.
Markovic-Pekovic V, Skrbić R, Godman B, Gustafsson LL.
Expert Rev Pharmacoecon Outcomes Res. 2012 Oct;12(5):661-71. doi: 10.1586/erp.12.48.

Increasing incidence of rubella in Republika Srpska in the period 2006-2010.
Cejić V, Naumović T.
Med Glas (Zenica). 2012 Feb;9(1):109-11.
PMID: 22634919 [PubMed - indexed for MEDLINE]

[Idiopathic scoliosis].
Jandrić S.
Med Pregl. 2012 Jan-Feb;65(1-2):35-40. Review. Serbian.

Digital clubbing as an unusual complication of the secondary hyperparathyroidism associated with atypical neutrophils: a case report.
Prodanovic N, Spiric Z, Trninic G, Eric M.
Eur Rev Med Pharmacol Sci. 2012 Oct;16 Suppl 4:98-102.

Appearance of femoropopliteal segment aneurysms in patients with abdominal aortic aneurysm.
Maksić M, Davidović L, Tomić I.
Vojnosanit Pregl. 2012 Sep;69(9):783-6.

Risk factors for intraoperative arrhythmias in general surgery patients operated under general anesthesia: our one-year experience.
Dostić MP, Tomović MT, Popović-Milenković MT, Stefanović SM, Janković SM.
Med Glas (Zenica). 2012 Aug;9(2):204-10.

The incidence of type 1 diabetes in Republic of Srpska (Bosnia and Herzegovina) and Slovenia in the period 1998-2010.
Radosevic B, Bukara-Radujkovic G, Miljkovic V, Pejicic S, Bratina N, Battelino T.
Pediatr Diabetes. 2012 Aug 28. doi: 10.1111/j.1399-5448.2012.00898.x. [Epub ahead of print]

Jožef Stefan and the dissolution-diffusion phenomena--not only a historical note.
Mitrovic J.
Int J Pharm. 2012 Jul 15;431(1-2):12-5. doi: 10.1016/j.ijpharm.2012.04.021. Epub 2012 Apr 13.

[Diclofenac induced liver injuries].
Nezic L, Krähenbühl S, Rätz Bravo AE.
Praxis (Bern 1994). 2012 Mar 14;101(6):371-9. doi: 10.1024/1661-8157/a000880. Review. German.

Galactocele in male infants: report of two cases and review of the literature.
Vlahovic A, Djuricic S, Todorovic S, Djukic M, Milanovic D, Vujanic GM.
Eur J Pediatr Surg 2012; 22(3): 246-250

Necrobiotic cutaneous granulomas in Nijmegen breakage syndrome.
Pasic S, Kandolf-Sekulovic L, Djuricic S, Zolotarovski L, Simic R, Abinun M. J Investig Allergol Clin Immunol 2012; 22: 138-140

Similar developmental patterns of ghrelin- and glucagon-expressing cells in the human pancreas.
Vignjević S, Todorović V, Damjanović S, Budeč M, Mitrović O, Djikić D, Drndarevic N, Mićić M, Mišković-Krivokapić J, Djuričić S, Nikolić I.
Cells Tissues Organs 2012; 196: 362-373

Prognostic value of surviving expression in Wilms tumor.
Basta-Jovanovic G, Radojevic-Skodric S, Brasanac D, Djuricic S, Milasin J, Bogdanovic L, Opric D, Savin M, Baralic I, Jovanovic M.
J BUON, 2012; 17: 168-173

Tamsulosin efficiency in treatment of benign prostatic hyperplasia evaluated by determining bladder weight.
Milicevic S.
Med Arh. 2012;66(6):391-5.

Role of hereditary factors in strabismus occurrence.
Regoda V, Sefic-Kasumovic S.
Med Arh. 2012;66(6):418-9.

Hemodynamics of arterial and venous circulation in the intrauterine fetal evaluation.
Cancarevic Djajic B, Vilendecic R, Ecim-Zlojutro V, Lucic N, Draganovic D, Savic S.
Acta Inform Med. 2012 Dec;20(4):249-53. doi: 10.5455/aim.2012.20.249-253.

[Assessment of recombinant human thyrotropin application in following-up patients with well-differentiated thyroid carcinoma].
Rajkovaca Z, Kovacević P, Stanetić M, Ristić S.
Vojnosanit Pregl. 2012 Nov;69(11):941-6. Serbian.

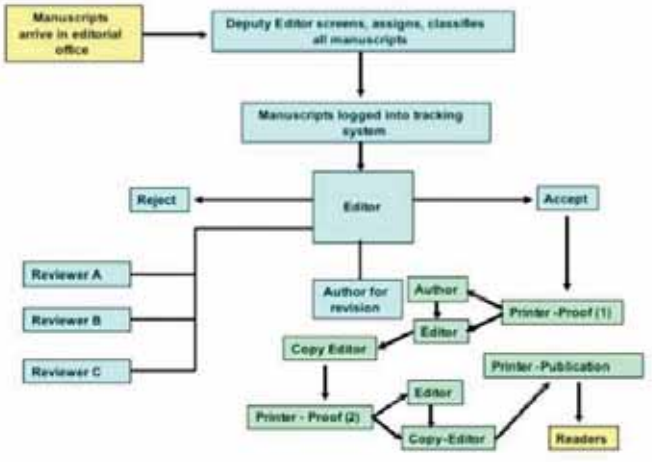
First-psychotic episode in childhood and adolescence.
Radmanović MB.
Psychiatr Danub. 2012 Oct;24 Suppl 3:S388-91.

Recenziranje rukopisa naučnih saopštenja

Recenziranje je proces procene vrednosti rukopisa naučnih saopštenja, procene koju daje stručnjak za područje istraživanja. Uloga recenzenta je dvostruka: on uredniku časopisa daje mišljenje o tome da li je rukopis pogodan za objavljivanje, a autorima, osim procene rada, često pomaže da poboljšaju rukopis. Ovde opisujemo proces recenziranja, izgled recenzije, osnovna svojstva objektivne i konstruktivne recenzije, primere recenzija i odgovore autora koje su uputili uredniku.

Rad na rukopisu od prijema u redakciju do publikovanja

Kada rukopis stigne u redakciju, najpre se procenjuje da li odgovara zahtevima časopisa koji su navedeni u uputstvu autorima. Ako je ta ocena zdovoljavajuća, većina biomedicinskih časopisa šalje rukopis recenzentima, stučnjacima koji dobro poznaju to područje. Nakon eventualnih izmena, dopuna i prihvatanja rukopisa sledi niz postupaka pre njegovog publikovanja (Slika 1).



Slika 1. Redosled rada na rukopisu, od njegovog prijema u redakciju do publikovanja.[1] Sličan je postupak kada časopis izlazi samo u elektronskom obliku.

Posle zadovoljavajuće inicijalne ocene rukopisa, koju daje glavni urednik časopisa (ponekad uz konsultaciji sa članom redakcionog odbora), traži se da recenzenti daju kompetentno i objektivno mišljenje o kvalitetu rada. One rukopise koji ne ispunjavaju zahteve časopisa urednik odbija i oni se vraćaju autorima bez slanja recenzentima. U toj fazi poznati međunarodni časopisi odbace do 90% rukopisa. Manji časopisi, zbog nedovoljnog broja kvalitetnih rukopisa, imaju daleko blaži kriterijum. Da bi popravili rukopise, urednici ponekad drže kurseve potencijalnim autorima, a neki im pomažu pri planiranju istraživanja i sastavljanju rukopisa. Dešava se da urednici objave priručnike kako bi autorima olakšali završni deo istraživačkog procesa.[2]

Recenzent prihvata ili odbija da obavi recenziju. Ako je prihvati, rok da se ona završi nikada nije duži od mesec dana. U slučaju da recenzent ne prihvati ponudu urednika, on tu odluku hitro saopštava uredniku kako bi se što pre našla zamena. Recenzent ne navodi razlog neprihvatanja tog posla, ali je najčešće u pitanju prezauzetost, izbegavanje procene zbog konflikta interesa, ili taj stručnjak ne želi da posveti vreme proceni nekvalitetnog rukopisa. Poznat britanski časopis BMJ ima na spisku oko 2.500 recenzenata.[3] (Uvek se traže novi, na osnovu objavljenih radova i preporuka, a odbacuju se loši recenzenti.)

Recenziranje je privilegija i odgovornost.[4] Od recenziranja imaju korist časopisi, autori rukopisa i sami recenzenti. Časopisi izuzetno retko plaćaju recenzente, ali se recenzentima često odaje javna zahvalnost tako što se u časopisu na kraju godine objave imena svih recenzenata. Takve spiskove mali časopisi, koji izlaze samo nekoliko puta godišnje, obično ne objavljuju jer bi autori lako otkrili ko je bio recenzent. Recenzent pomaže časopisu, a istovremeno pruža doprinos nauci, jer takav rad obezbeđuje kvalitet publikacija. Sem toga, recenzent ima i neposrednu korist jer prvi sazna rezultate koji se nalaze u rukopisu i to mu pomaže u vlastitom radu. Međutim, nije etički da recenzenti preuzmu bilo kakvu ideju ili podatak iz rukopisa koji recenziraju. Tek kada se taj rad objavi u časopisu, oni ga mogu citirati u svojim publikacijama. Recenzenti su dužni da drže u tajnosti podatke iz rukopisa.

Izgled recenzije

Neki časopisi zahtevaju da se izveštaj recenzenta (recenzija) dostavi u dva dela: 1) pismo upućeno uredniku i 2) izveštaj koji će urednik uputiti autoru. U pismu uredniku se navodi ime recenzenta, naslov rukopisa i predlog uredniku (da se rukopis prihvati, odbije, preuredi, dopuni novim eksperimentima, itd.). Odnedavno sva korespondencija autora, urednika i renzenata obavlja se elektronski i sve je više časopisa koji ne zahtevaju od recenzenta posebno, poverljivo mišljenje o radu.

Urednik recenziju šalje autoru, a ponekad i drugom recenzentu. Recenzija je anoniman dokumenat za autora i za drugog recenzenta. Izuzetak su recenzije otvorenog tipa. Recenzija obično sadrži nekoliko delova. Najpre se u jednom pasusu sumira (bez kritike) ono što je uradjeno u radu. Drugi segment sadrži opštu ocenu (važnost istraživačkog pitanja, originalnost rada, jake i slabe strane metodologije, eksperimentalnog dizajna, ocenu statističkog pristupa i interpretacije rezultata). Zatim sledi konstruktivna kritika pojedinih delova rukopisa i na kraju se iznose manje tekstualne i gramatičke greške. Na ove poslednje

primedbe se često samo ukazuje, a urednici će kasnije detaljno korigovati te nedostatke. U zaključku se daje ukupna ocena rukopisa. Sekcije koje se često sreću u recenzijama date su u nastavku.[5]

Struktura recenzije
- *Sumiranje rukopisa (istraživački problem, cilj istraživanja, zaključak koji su dali autori)*
- *Opšta ocena rukopisa*
- *Konstruktivna kritika (ukazuje se na ono što bi trebalo da se unapredi u svakom poglavlju rukopisa)*
- *Male (minorne) greške*
- *Zaključak*

Kako recenzent procenjuje rukopis?
Najbolje je da recenzent posebno proceni svaki deo rukopisa. Ovde ukratko opisujemo kako se daje sistematska procena rukopisa empirijskih istraživanja. Ta istraživanja mogu biti kvantitativna (mahom eksperimentalne studije) i kvalitativna. Ova poslednja vrsta istraživanja je danas značajno unapređena i sve češće se primenjuje u nekim biomedicinskim disciplinama.[2]

Naslov. Preopširan ili nedovoljno informativan naslov se ponekad sreće u rukopisima koje pripremaju početnici, ali se dešava da i iskusniji autori načine grešku. Zato recenzent pažljivo pregleda naslov na samom početku i ponovo na kraju čitanja rukopisa.

Apstrakt. Dobro napisan apstrakt oraspoloži recenzenta. Međutim, ako apstrakt sadrži više problema, to će se negativno odraziti na mišljenje o rukopisu.

Najvažnije odlike apstrakta na koje obraca pažnju recenzent
- *Dužina apstrakta (nestrukturisan do 150 reči, strukturisan do 250 reči)*
- *Da li je jasna hipoteza ili cilj istraživanja*
- *Jesu li navedene metode kojima se došlo do cilja istraživanja*
- *Da li rezultati pokazuju da je postignut cilj istraživanja*
- *Da li je zaključak zasnovan na dobijenim rezultatima*
- *Da li se stiče utisak da je reč o važnom istraživanju i da li je ono originalno*

Uvod. Recenzent će u uvodu steći još bolji ili lošiji utisak o onom što je saznao iz apstrakta. Najvažniji deo uvoda je cilj saopštenja. tj. pitanje koje je navelo autora na istraživanje. Recenzent proverava da li je i kako autor naveo šta nedostaje naučnom znanju i šta je potrebno istraživati, procenjuje da li se u uvodu naznačava kako se prišlo rešavanju postavljenog pitanja. On očekuje da su u uvodu citirani samo radovi koji su neophodni za odgovarajuće tvrdnje, a ne želi da vidi podatake i zaključke do kojih je došao autor u ovom istraživanju.

Metode. Recenzent obraća pažnju na dizajn studije, veličinu grupa (laboratorijskih životinja, pacijenata i odgovarajućih kontrola), ocenjuje da li su tehnike zastarele i da li je statistička analiza odgovarajuća. Procenjuje kako su autori odredili veličinu uzorka i da li je naveden metod procene, nivo signifikantnosti (na primer, P<0.05 ili P<0.001) i statistička snaga (na primer, 80% ili 90%). Posebnu pažnju recenzent obraća na to jesu li pravilno korišćeni SD, SE i interval pouzdanosti (Cofidence Intervals, CI).[2] Manjkavost nastaje kada se statistička hipoteza testira samo pomoću P vrednosti, a nedostaju kvantitativne informacije.[6] Opis statističkih metoda treba da je u poglavlju metode, a kada se iznose podaci u poglavlju rezultati navode se statističke metode pomoću kojih su analizirani podaci. Najbolje je kada statističku procenu rukopisa izvrši i urednik za statistiku ili član uređivačkog odbora koji je ekspert za biomedicinsku statistiku.

Segment teksta u poglavlju materijal i metode u kome se opisuje velicina uzorka[7]
Koristeći NQuery statistical power software (Statistical Solutions, Cork, Irelad), procenili smo da se na uzorku od šest osoba može ustanoviti razlika srednje vrednosti 50% nivoa proteina bazalnog mišićnog toplotnog šoka koji se javlja kod treniranih i netreniranih osoba pod pretpostavkom da je SD razlika jednaka 25% i statistička snaga 80%. Ta veličina efekta i SD su zasnovane na vrednostima ranijih ispitivanja u kojima je istraživan nivo proteina kod mišićnog toplotnog šoka.[19,20].

Rezultati. Recenzent s posebnom pažnjom procenjuje da li su rezultati prikazani u logičnom sledu teksta, tabela i ilustracija. Osim toga, on će ustanoviti da li postoji nepotrebno ponavljanje podataka u tekstu, ako su isti rezultati prikazani u tabelama i ilustracijama.

Diskusija. U diskusiji treba naglasiti važne aspekte studije i zaključke koji iz njih proizilaze. U njoj ne treba ponavljati ono što je dato u uvodu ili rezultatima. U diskusiji treba navesti implikacije, ali i ograničenja studije. Zapažanja treba uporediti s odgovarajućim relevantnim studijama. Poseban problem je kada diskusija sadrži neadekvatnu hipotezu, nejasne i nepotkrepljene tvrdnje, krivu interpretaciju literature da bi se potvrdila autorova pretpostavka i kada se ne diskutuje o anomalijama.

Reference. Na nepravilan izled referenci se ukazuje autoru već pri početnoj proceni rukopisa. Urednici časopisa na te nepravilnosti samo ukazuju, a dužnost je autora da ih ispravi pre nego što se rukopis šalje recenzentima. Recenzent procenjuje koji su radovi citirani u uvodu, a koji u diskusiji, da li su uključene samo stare publikacije, da li u spisku referenci ima previše nepotrebnih samocitata i da li je prevelik ili nedovoljan broj citata. U apstraktima, gotovo redovno, treba izbegavati citate.

Recenziranje revijskog članka
Rukopis revijskog članka treba da sadrži poglavlje koje opisuje metode kojim su nađeni, odabrani i sintetisani podaci. Ti se metodi moraju opisati i u apstraktu. Od naslova, preko apstrakta, tekstualnog dela, ilustracija i tabela do eventualne diskusije i referenci procena je slična proceni radova u kojima se saopštava originalno istraživanje.

Odgovor autora uredniku na primedbe recenzenata
Kada autor od urednika časopisa primi izveštaje recenzenata i odluku urednika, on treba da odgovori na svaku, eventualnu, kritiku i sugestiju recenzenta i urednika. U nastavku je dat primer odluke urednika koja je upućena autoru.

The large number of manuscripts received by Surgical Laparoscopy, Endoscopy & Percutaneous Techniques necessitates a rigorous selection process. Reviewers of your manuscript have not granted it priority for publication. Regretfully, therefore, we have to reject your manuscript. Copies of the reviews from the review board are enclosed. Please feel free to address the suggested revisions, revise your paper and resubmit it for publication. Please include with your revised submission an itemized, point-by-point response to the comments of the reviewers. The revisions should be completed by 12/30/2012 to avoid being considered as a new submission.

Ukoliko su u pitanju samo minorne primedbe koje su uputila oba recenzenta (to se izuzetno retko događa) i urednik donese odluku da se rad objavi, rukopis se u nekim časopisima ne vraća autoru na korekcije. Urednik obavesti autora da je rad prihvaćen, a male jezičke i druge izmene autor će proveriti kada dobije na uvid probni otisak. Kada oba recenzenta predlože da se rukopis odbije, urednik se većinom s tim predlozima saglasi. On šalje autoru obe recenzije da mu posluže kako bi sagledao nedostatak istraživanja. Ako ne postoji saglasnost dva recenzenta o važnijim pitanjima, urednik će eventualno angažovati trećeg recenzenta da proceni rukopis ili će i bez treće recenzije doneti odluku. Kada je reč o važnijim primedbama recenzenata, urednik ispravke koje je uradio autor šalje na uvid recenzentima. Zato se od autora traži ne samo da drugačijom bojom slova označi promene koje je uneo u originalni rukopis, već da u posebnom dopisu navede šta je povodom svake primedbe recenzenata uradio. To je pomenuti „itemized, pointbypoint response to the comments of the reviewers". Takva objašnjenja pomažu uredniku, a često i recenzentima, da sagledaju šta (ni)je, zašto i kako u rukopisu izmenjeno.

***Primer odgovora autora na primedbe recenzenata koji je poslao uredniku časopisa*[2]** (Tri recenzenta su dala na desetine primedbi autorima rukopisa, a ovde se navode samo dve-tri.)

Recenzent #2:
Diskusija je nepotrebno preopširna, treba je skratiti.

Autor:
Diskusiju smo skratili i označene pasuse izostavili...

Recenzent #3:
Permanentna bilateralna okluzija karotidnih arterija u pacova je često korišćen metod u istraživanju hronične cerebralne hipoperfuzije kod različitih neurodegenerativnih procesa, uključujući starenje i Alzheimerovu bolest. Pitanje je da li je taj model pogodan za ispitivanje propadanja dopaminergičkih neurona nakon cerebralne hipoperfuzije kod glodara da bi poslužio kao pogodan model za Parkinsonovu bolest. Autori nisu naveli da li je kod životinja došlo do pojave tremora i drugih znakova parkinsonizma.

Autor:
Mi nismo vršili bihevioralno testiranje jer primećene promene mogu biti zbog gubitka dopamina ili efekta hronične hipoperfuzije mozga...

Recenzent #3:
Naslov rukopisa treba promeniti. Iz njega treba izostaviti ove reči „Vaskularni parkinsonizam, Parkinsonova bolest i starost".

Autor:
Naslov rukopisa smo promenili kako je predložio recenzent.

Neki autori nisu upoznati kako se odgovara na pitanja i primedbe koje daju recenzenti. Tako smo u *Scripta Medica* od jednog autora rukopisa zaduženog za korespondenciju (Corresponding Author), umesto detaljnog obrazloženja izmena primili ovakav odgovor na primedbe dva recenzenta i lektora engleskog jezika:

Uradili smo i ispoštovali sve što je tražio recenzent I (naročito on), recenzent II (koji je dao i dosta nepotrebnih komentara) i III lektor.

*Korigovano je sve što su sugerisali koautori (*ovde se navode imena dva koautora s njihovim titulama*), čije mišljenje cjenim više od svih navedenih recenzenata.*[1]"

Neprihvatanje neke od primedbi recenzenta autor mora da objasni. Nema razloga da se autor ljuti na recenzente ako mu rad lošije ocene nego što je očekivao. Nakon odbijanja rada autor nikada ne treba da se žali uredniku ili časopisu. On može taj rad da pošalje drugom časopisu. Recenzenti, a često i urednici, jesu naučnici koji odvoje deo svog dragocenog vremena da bi obavili taj, za progres nauke važan posao. Da bi se izbegli previdi jednog recenzenta, časopis šalje rukopis da ga ocene dva, a nekada i

[1] *Recenzent #1 je veoma ugledan profesor fiziologije. On je dao seriju korisnih predloga da se rukopis stručno i jezički poboljša. Recenzent #2 je profesor biohemije i specijalista jedne kliničke discipline. Oni su istraživači koji rade na dva različita univerziteta u SAD.*

tri recenzenta. Osim recenzenata, i urednici pregledaju i ocenjuju svaki rad.

Da bi svi autori na vreme pregledali rukopise koji pristignu u redakciju *Scripta Medica* i dali saglasnost da mogu biti objavljeni, u uputstvu autorima se – kao što to odnedavno zahtevaju mnogi međunarodni časopisi – traži od svih autora (ako ih je dva ili više) da potpišu izjavu o autorstvu.[8] Naime, svako od njih treba da opiše doprinos radu i tu izjavu potpiše. (Nedavno se dogodilo u jednoj bivšoj jugoslovenskoj republici da ugledan professor dopiše stranog autora u plagiran rukopis i bez znanja tog pojedinca rad objavi u međunarodnom časopisu.[1] Pojedinac je za tu „svoju publikaciju" saznao tek kada je plagijat otkriven.) Osim toga, u propratnom pismu treba da se navede sledeće:

- *rad nije ranije publikovan i nije istovemeno podnet za objavljivanje u nekom drugom časopisu,*
- *svi su autori pročitali rukopis i odobrili ga*
- *pismena saglasnost ili dozvola je pribavljena od svih osoba koje se pominju u poglavlju zahvalnost, itd.*[2]

Kako časopis procenjuje recenzije i recenzente?

Časopis procenjuje kvalitet recenzenta tako što se proceni: 1) da li je pristup oceni rukopisa izveden seriozano, 2) da li se citiraju dokazi kako bi se potkrepila kritika koja se šalje autoru, 3) da li je kritika rukopisa konstruktivna i ocena objektivna, 4) da li je predlog uredniku jasno obrazložen i 5) da li je recenzent na vreme uradio recenziju.

U nastavku su dve recenzije. Prvi primer sadrži četiri kratka dela (sekcije), a drugi je napisan u jednom pasusu; ovaj poslednji je površni prilaz recenziranju.

Prvi primer

The manuscript by Banegas et al. presents the data that show an inhibitory influence of the dopaminergic pathways in the brain of the rat. The authors stated that reduced activity of these enzymes may modify metabolism of various endogenous substrates that could affect their function in the brain. The MS addressed important topic; however, the following issues should be clarified.

Major remarks

1. In this study only left brain samples were used—both in the controls (n=4) and lesioned (n=7) rats. Why did the authors exclude the regions at the opposite side of the brain? Such data might represent an additional valuable control.
2. Please, check the statistical analysis because the *P* value for the CysAP in the perifrontal cortex seems to be smaller than 0.01 or even <0.001; also, the AlaAP activity in the *S. nigra* the *P* value seems to be smaller than 0.05 or it is N.S.
3. When the activity of some enzymes that inactivate a peptide due to the lesion is changed, its release may also be altered. We do not know what is the net change (if any) of the peptides that might be affected in the lesioned regions, and it is not necessary to discuss extensively their contribution to certain functions of the brain. Thus, discussion may be much shorter and focused on the data obtained.
4. The activities of all AP studied were not reduced "by 50% or even more in the brain structures studied" – as it is stated in the Abstract, Results, and Discussion. See in the Fig. 1 values for striatum (CysAP, AspAP and GluAP).

Minor remark

The supplier or the source of the substrates should be stated.

Conclusion

After clarifications and corrections, this paper could be published as a Short Publication.

Drugi primer

Pažljivo sam pročitao rukopis i nalazim da je rad sasvim korektan. Rad nema prevelike pretenzije već želju da ukaže na jedan aspekt problema o kome se malo vodi računa. Metoda je relativno nova i svako saopštenje je dragoceno, pogotovo ako je sa naših prostora, što po mome mišljenju treba ohrabriti. Shematski prikazi. tj. grafikoni mogu na prvi pogled izgledati kao suvišni. ali vizuelni utisak ima određene prednosti nad tekstualnim. Rad ima određenu edukativnu ulogu za stručnjake ove discipline jer daje korisnu informaciju, Međutim, reference treba srediti prema strogim pravilima i autore treba uputiti u Univerzitetsku biblioteku jer to je posao od desetak minuta (zameniti zareze tačkama, definisati način za originalni rad, deo u udžbeniku i sl.) Po mome mišljenju rad slobodno može ići u štampu.

Kako pronaci dobre recenzenate?

Kvalitetne recenzije značajno doprinose kvalitetu publikacija u časopisu. Zato bi bilo korisno kada bi urednici mogli unapred da znaju ko su dobri recenzenti ili kako bi se recenzenti mogli usavršiti da bolje procenjuju rukopise. U jednoj studiji su učestvovala 308 recenzenata s ciljem da se ustanovi da li specijalne vežbe, odgovarajući akademski nivo ili iskustvo u pisanju naučnih projekata utiču na kvalitet recenziranja. Ustanovljeno je da su epidemiolozi, stručnjaci koji poznaju statistiku i oni stručnjaci (bilo koje discipline) koji su bili članovi nekog uređivačkog odbora časopisa bolje procenjuju rukopise.[4] Postoji opšta saglasnost da su najbolji recenzenti istraživači koji su publikovali radove u časopisima. (Ovde se ne ubrajaju oni čija se imena samo dopisuju u publikacijama ili im je doprinos u objavljenim radovima bio minimalan.) Dakle, autori čiji su rukopisi više puta recenzirani u dobrim časopisima imaju iskustvo koje im pomaže da budu dobri recenzenti.

Da se proces recenziranja ujednači, neki časopisi ponekad dostave recenzentima formulare koji pomažu da se rukopis oceni, u celini i u pojedinim delovima, te da se dođe do ocene i preporuke o publikovanju rukopisa. Međutim, ti formulari nisu garancija da će svi recenzenti *lege artis* obaviti procenu. Zato časopisi iz spiska recenzenata izbacuju loše recenzente, tj. ne angažuju ih ponovo. *Scripta Medica* ima trogodišnje iskustvo u redovnom recenziranju rukopisa. Neke su recenzije veoma kvalitetne, ali je bilo i površnih.

Pri recenziranju je neophodno izbeći sukob interesa. Nije dozvoljeno da recenzent bude iz iste institucije iz koje je prispeo rukopis ili ako su recenzent i autor bilo kad publikovali zajednički članak. Te okolnosti može proceniti redakcija časopisa, ali i sam recenzent može navesti da zbog sukoba interesa ne prihvata da proceni rukopis. Neki časopisi traže od autora da načini spisak od pet-šest stručnjaka koji su potencijalni recenzenti. Taj način izbora recenzenata se danas koristi sve ređe.

[2b] *Scripta Medica 2012;43:32-3.*

Anonimno ili otvoreno recenziranje?

U naučnim krugovima i na međunarodnim sastancima posvećenim publikovanju biomedicinskih časopisa bilo je puno debata o anonimnosti recenzenata. U malim sredinama koje izdaju lokalne biomedicinske časopise, otvorene recenzije bi imale seriju nedostataka. Retko koji bi recenzent želeo da se javno eksponira kad piše negativnu recenziju lokalnom autoritetu, mada bi otvorena procena vrednosti rukopisa stavljala pred recenzenta veću stručnu i etičku odgovornost pri kritici i predlozima da se rukopis poboljša. Zato anonimost recenzenata u takvim sredinama, ipak, ima prednost; tim više što se tako olakšava posao urednicima kada donose odluke da rukopise ne objave.

Rajko Igić, glavni urednik
Aleksandar Lazarević urednik
Stevan Trbojević, urednik

Reference

1. Igić R. Publication in peer-reviewed journals. *Journal of BUON* 2006;11:405-10.
2. Igić R, Škrbić R. *Kako se pišu i publikuju saopštenja o biomedicinskim istraživanjima*. Banja Luka/Laktaši, GrafoMark, 2012.
3. Anonimus. Recenziranje rukopisa. *Kontakt* (Novi Sad) 1998;6:1-2.
4. Benos DJ, Kirk KL, Hall JE. How to review a paper. *Adv Physiol Educ* 27;47:-52, 2003.
5. Hall GM (ed.). *How to write a paper*. Malden, Blackwell, 2008.
6. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med* 1997; 336:309-16.
7. Morton J P. Reviewing scientific manuscripts: how much statistical knowledge should a reviewer really know? *Adv Physiol Educ* 2009:33:7-9.
8. Anonimus. Uputstvo autorima za pripremu rukopisa. *Scr Med* 2012;43:132-5. www.scriptamedica.com (free access).

Uputstvo autorima za pripremu rukopisa

Scripta Medica (SM) je internacionalni časopis Društva doktora Republike Srpske koji objavljuje originalne članke (klinička, laboratorijska i epidemiološka istraživanja), ali i članke koji maju za cilj da edukuju i obavijeste ljekare i stručnjake drugih biomedicinskih disciplina. SM, kao opštiemedicinski časopis, daje prednost rukopisima o originalnim kliničkim istraživanjima. Na engleskom jeziku časopis objavljuje originalne radove, pregledne članke, specijalne članke, rješavanje kliničkog problema, prikaze slučajeva, slike iz kliničke medicine, istorijske članke i eseje. Samo na srpskom se objavljuju prikazi knjiga, vijesti, izvještaji sa naučnih skupova, kraći edukativni i drugi članci. Časopis je svima, bez naknade, dostupan na internetu (www.scriptamedica.com).

Opšta uputstva

1. Rukopis
Rukopis rada treba dostaviti u .DOC formatu (Microsoft Word, Times New Roman font, večina slova 11 *pt*). Glavni naslov kucati slovima veličine od 12 *pt* **bold,** a naslove poglavlja slovima od 11 *pt* **bold**. U tabelama koristiti slova veličine 10 *pt*, jednostruki prored, a naslovi unutar tabela treba da su veličine 10 *pt* **bold**; za glavni naslov tabele koristiti 12 *pt* **bold**; legende se ispisuju jednostrukim proredom slovima od 11 *pt*. Illustracije se dostavljaju u JPG ili TIFF formatu (300 dpi ili bolja rezolucija).

2. Za lijekove i hemikalije koristiti generičke nazive. Za instrumente, aparate i ostale uređaje dati njihove nazive, a u zagradi dati nnavesti proizvođača i grad.

3. Brojeve koji su manji od deset u tekstu treba ispisati rečima, a za 10 i više koristiti numeričku oznaku. Brojeve u tekstu i tabelama treba navesti za vrednosti od koji su načinjene procentualne vrednosti; iza srednje vrednosti stoji standardna devijacija (SD), a iza medijana međukvartalni raspon (interquartile range, IQR).

4. Naslov slike treba da je veličine 10 *pt* **bold**; legende kucati jednostrukim proredom, slovima veličine 10 *pt*.

5. Reference se u tekstu označavaju brojevima ispisanim superskriptom iza bilo kog znaka interpunkcije.

6. Jedinice mere, dužine, težine i zapremine izražavaju se metričkim jedinicama (na primer, metar—m, kilogram—kg, litar—l) ili njihovim delovima. Temperaturu izražavati u stepenima Celzijusa (^{o}C); količinu supstance u molima (mol), a pritisak u milimetrima živinog stuba (mm Hg). Sve vrednosti hematoloških, kliničkih i biohemijskih merenja navoditi u metričkom sistemu prema Međunarodnom sistemu mera (International System of Units, SI units).

7. Skraćenice koristiti samo za duge nazive, uključujući imena hemijskih supstancija. Pun naziv dati kada se isti pojavi prvi put u tekstu, ukoliko to nije standardna jedinica mere. Ako se skraćenice koriste u Apstraktu, svaku treba objasniti kada se prvi put pomene u tekstu. Za opštepoznate skraćenice, kao što su DNK, SIDA, HIV, ATP, ADP, ne treba uvoditi pun naziv. U naslovu članka mogu se naći samo opštepoznate skraćenice.

8. Izjava o autorstvu. Da bi se istraživač kvalifikovao za autora, mora dati značajan intelektualni doprinos studiji koja je osnova za članak (WAME.com, Policy Statements—Authorship). Autor mora učestvovati barem u jednoj aktivnosti u svakoj od tri sledeće kategorije:

a. postavljanje istraživačkog pitanja, izrada koncepta i dizajna studije, prikupljanje i analiza podataka,
b. statistička analiza, interpretacija podataka, obezbeđenje sredstava za istraživanje, administartivna, tehnička ili materijalna podrška, nadgledanje celokupnog toka istraživanja,
c. pisanje prve verzije ili kritička revizija rukopisa.

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Bosnia i Herzegovina
Telefon i faks: +387-(51) 329-100
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Prevod apstrakta, tabela i naslova ilustracija na engleski. Na posebnoj stranici priložiti naslov rada na engleskom jeziku, imena i prezimena autora (bez titular) indeksirana brojevima, zvanični naziv ustanova na engleskom jeziku, *structured Abstract* (Introduction, Methods, Results, Conclusion). Prevesti nazive tabela, slika i celokupni tekst u njima. Treba se pridržavati jezičkog standarda British English. [Radovi koji se u celini dostave na engleskom imaju prednost u objavljivanju. Uputstvo za rukopise na engleskom dato je u *Instructions for contributors*.]

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Materijal i metode. Ovo poglavlje opisuje procedure pomoću kojih se izvodi studija; opis treba da omogući drugima, ako žele, da studiju ponove. Ako je metod merenja poznat, treba ga citirati i opisati s par rečenica. Treba prikazati dizajn studije i navesti koje su intervencije preduzimane, da li postoji saglasnost etičkog komiteta o eksperimentima na ljudima i višim životinjama, kako je vršena randomizacija, koliko dugo su praćeni učesnici, kako su prikupljani podaci i kako je vršena statistička analiza podataka. Treba definisati nezavisne i zavisne varijable. Za lekove i hemikalije koristiti generičke nazive, doze lekova i način davanja. Variabilnost izraziti pomoću srednje vrednosti i standardne devijacije (SD). Pošto su SD i standardna greška srednje vrednosti (SE) pozitivni brojevi, *Council of Science Editors* preporučuje eliminaciju znaka +/- sign; umesto njega SD, kao i SE, se daju u zagradama. Na primer, "sistolni krvni pritisak grupe zdravih studenata iznosio je 129 mm Hg [SD = 6, n = 87]." Vrednost P može se koristiti da se odbaci nulta hipoteza, ali treba navesti

procenu snage studije (power of the study) i statistički test korišćen u statističkoj analizi.

U revijskim (preglednim) člancima se opisuju metode kojima su locirani, odabrani, pronađeni i sintetisani podaci. Te metode, takođe, treba navesti u apstraktu.

Rezultati. Dobijene rezultate treba izložiti logičkim tokom korišćenjem teksta, tabela i ilustracija. Sve ilustracije nose naziv "Slike" (Figures). Taj deo rukopisa daje odgovor studije na postavljeno istraživačko pitanje. Ponekad je to najkraći tekstualni deo rukopisa. Detalji se mogu prikazati u jednoj ili više tabela i slika. Ne ponavljati podatke iz tabela ili slika u tekstu. U tekstualnom delu treba samo naglasiti najvažnije rezultate koji direktno odgovaraju na pitanje iz Uvoda.

Tabele. Svaka tabela (4 tabele ili slike su dozvoljene) sa svojim legendama treba da opiše o čemu je reč; redosled im se numeriše arapskim brojevima u tekstu. Naslov treba da je iznad tabele, a objašnjenja, uključujući definicije skraćenica, nalaze se ispod tabele. Sve ovo pisati dvojezično (srpski i engleski). Tabele raditi isključivo u programu *Word* (koristiti *table-insert-table*). U tabeli, u iste ćelije uneti tekst na srpskom i engleskom jeziku. (Nikako ne praviti dve dabele na dva različita jezika.)

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Reference. Ispravnost liste referenci je odgovornost autora. Citirati članke u tekstu rednim arapskim brojevima prema redosledu navođenja u tekstu. Reference se ispisuju prema Vankuverskom stilu—broj se u tekstu navodi u superskriptu, nakon bilo kog znaka interpunkcije. Na primer, Vulić and colleagues.[12] Kada se citiraju dve reference, one se odvajaju zarezom, bez razmaka. Tri ili više referenci u nizu se razdvaja crtom (na primer, [3-6]). Reference koje se eventualno citiraju u tabelama i slikama dobijaju redni broj prema mestu gde se ove ilustracije postave u tekstu. Za citiranje prema Vankuverskom stilu, videti *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*; to su pravila koja su data od strane Međunarodnog komiteta urednika medicinskih časopisa (International Committee of Medical Journal Editors; www.icmje.org). Ako referenca sadrži šest autora ili manje, treba navesti sve autore prezimenom, razmak, inicijali, zarez. Ako u pitanju sedam ili više autora, navode se prva tri i sledi *et al.* U nastavku su primeri navođenja nekih publikacija, a za ostale uputstvo je na internet stranici: (www.nlm.nih.gov/bsd/uniform_requirements.html).

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

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, Čolić M, et al. Treatment of traumatic rupture of the thoracic aorta. Srp Arh Celok Lek 2008;136:498-504.

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

Electronic publications (ove citate treba izbegavati):

International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info (accessed March 20, 2012).

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfield.libraryupenn. edu/essays/v13p019y1990.pdf (accessed Dec 25, 2011).

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Da se izbegnu kašnjenja, preporučujemo autorima da sve potpisane dokumente pošalju zajeno s rukopisom.

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- PROPRATNO PISMO
- IZJAVA O AUTORSTVU
- IZJAVA O KONFLIKTIMA INTERESA

Instructions For Contributors

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3. Numbers in text and tables should be provided if expressed as %; means should be accompanied by SDs, and medians by interquartile range (IQR). In text, use following rule: spell out numbers up to ten and then use numerical designation for 10 and above.

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5. References should be indicated in the text sequentially in the Vancouver numbering style, as superscripted number after any punctuation mark.

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Društvo doktora Republike Srpske
c/o Ms. Biljana Radišić
Prvog krajiškog korpusa 4/I
78000 Banja Luka, Republic of Srpska, Bosnia & Herzegovina
Phone & Fax: +387-(51) 329-100
E-mail: drmrs@inecco.net
editor@scriptamedica.com
www.scriptamedica.com

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

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, Čolić M, et al. Treatment of traumatic rupture of the thoracic aorta. Srp Arh Celok Lek 2008; 136: 498-504.

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

Electronic publications:

International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info Accessed March 20, 2012.

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfield.libraryupenn. edu/essays/v13p019y1990.pdf. Accessed April 25, 2012.

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