

## ZR1 – Međulaboratorijske usporedbe, ZR1-1

**Utjecaj harmonizacije općih medicinsko-biokemijskih pretraga na rezultate vanjske procjene kvalitete medicinsko-biokemijskih laboratorija**Flegar-Meštrić Z<sup>1</sup>, Juretić D<sup>2</sup><sup>1</sup>Zavod za kliničku kemiju, KB Merkur, Zagreb, Hrvatska<sup>2</sup>Zavod za medicinsku biokemiju i hematologiju, Farmaceutsko-biokemijski fakultet, Zagreb, Hrvatska

Uloga vanjske procjene kvalitete rada medicinsko-biokemijskih laboratorija (MBL) je osigurati neovisnu i objektivnu procjenu dobivenih rezultata kako bi se utvrdio stupanj razvoja struke i potaknuo postupak standardizacije svih procesa laboratorijskog rada s ciljem povećanja stupnja međulaboratorijske usporedivosti i harmonizacije u području laboratorijske dijagnostike. Analizom rezultata vanjske procjene kvalitete HDMB provedene u 3 ciklusa tijekom 2005. g. uočeno je da su se prosječni koeficijenti varijacije (KV%) za pojedine pretrage unutar svih laboratorija sudionika značajno smanjili: za urate sa 6% na 3% neprihvaćanjem metode urikaza-PAP bez askorbat oksidaze, a obveznom primjenom metoda IFCC za enzime za LDH s 22% na 5%, za CK sa 7% na 3%, za ALP sa 14% na 8%, za CHS s 31% na 8%, za aminotransferaze sa 7% na 4%. Rezultati međulaboratorijskih usporedba laboratorijskih pretraga za 174 laboratorija sudionika još uvijek pokazuju značajna odstupanja rezultata pojedinih MBL od srednje vrijednosti grupe, što ima za posljedicu veliku raspodjelu dobivenih rezultata. To potvrđuje da na konačan rezultat laboratorijske pretrage ne utječu samo razlike u primijenjenim analitičkim metodama, nego i različiti kalibratori i kontrolni materijali. Zato u cilju globalne harmonizacije Europska direktiva 98/79 za "in vitro laboratorijsku dijagnostiku" zahtijeva mjeriteljsku sljedljivost kalibratora i kontrolnih materijala uz iskazanu mjernu nesigurnost. Godišnje izvješće o rezultatima vanjske procjene kvalitete HDMB za 3 provedena ciklusa tijekom 2005. g. pokazalo je da prosječno 30% MBL zadovoljava postavljene analitičke ciljeve kvalitete sa 100% prihvatljivih rezultata, više od 60% MBL s više od 80% prihvatljivih rezultata, a manje od 10% MBL nije zadovoljilo postavljene analitičke ciljeve kvalitete. Rezultati vanjske procjene kvalitete rada MBL pokazali su pozitivan utjecaj primjene preporučenih analitičkih metoda na harmonizaciju laboratorijskih rezultata. U daljnjem radu uvođenje međunarodnog standarda ISO 15189:2003 za medicinske laboratorije omogućiti će harmonizaciju svih faza laboratorijskog procesa i time

## ZR1 – Interlaboratory comparisons, ZR1-1

**Impact of harmonization of general medical biochemistry analyses on external quality assessment results**Flegar-Meštrić Z<sup>1</sup>, Juretić D<sup>2</sup><sup>1</sup>Department of Clinical Chemistry, Merkur University Hospital, Zagreb, Croatia<sup>2</sup>Department of Medical Biochemistry and Hematology, School of Pharmacy and Biochemistry, Zagreb, Croatia

One of the main purposes of external quality assessment in medical biochemistry laboratories is to provide an independent and objective evaluation of laboratory test results in order to promote standardization of the overall laboratory process and achieve a high degree of inter-laboratory comparability and harmonization of test results in the field of medical biochemistry. Long-term evaluation of the results obtained in three surveys during 2005 showed a significant improvement of analytical quality in medical biochemistry laboratories. The coefficients of variation (CV%) for some analyses showed a decreasing tendency: for urates CV decreased from 6% to 3% with exclusion of the uricase-PAP method without ascorbate oxidase; for enzymes the obligatory use of IFCC methods decreased the CV for LDH, CK, ALP, CHS and aminotransferase from 22% to 5%, from 7% to 3%, from 14% to 8%, from 31% to 8% and from 7% to 4%, respectively. The inter-laboratory comparisons of laboratory test results for 174 participant laboratories showed significant result deviation from the mean of the group for some laboratories, resulting in wide distribution of the results obtained. These results indicate that laboratory test results are influenced not only by the analytical method used but also by different calibrators and control materials. Therefore, the European Directive 98/79 on *in vitro* medical devices (IVD) requires metrological traceability for standards and control materials with stated uncertainties. The annual report for the three surveys in 2005 showed that almost 30% of medical biochemistry laboratories achieved analytical goals with 100% of acceptable results, more than 60% laboratories fulfilled the requirements with more than 80% of acceptable results, and less than 10% of the laboratories were not able to meet the required analytical quality specification for diagnostic testing. External quality assessment in medical biochemistry laboratories in Croatia showed a positive effect of the recommended methods on the harmonization of laboratory results. In the future, the availability of an international standard,

postizanje najviših ciljeva kvalitete u laboratorijskoj dijagnostici.

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## ZR1-2

### Evaluacija rezultata u laboratorijskoj hematologiji

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Zavod za kliničku kemiju KB Merkur od 1985. g. sudjeluje u međunarodnoj sponzoriranoj kontroli iz laboratorijske hematologije – International External Quality Assessment Scheme for Haematology IEQAS-(H) pod pokroviteljstvom Svjetske zdravstvene organizacije (SZO), s obvezom aktivnog sudjelovanja u provođenju vanjske procjene kvalitete u Hrvatskoj. U okviru Povjerenstva za vanjsku procjenu kvalitete Hrvatskoga društva medicinskih biokemičara, od 1988. g. provodi Vanjsku kontrolu kvalitete iz laboratorijske hematologije. Cilj rada je pokazati rezultate nacionalne kontrole kvalitete iz područja laboratorijske hematologije tijekom 2005. godine s obzirom na postavljene ciljeve analitičke kvalitete. Na godinu se šalju 3 komercijalna pripravka krvi za određivanje hematoloških pretraga na hematološkim brojačima s trodijelnom krvnom slikom. Uzorak za retikulocite je razmaz napravljen iz venske krvi obojene briljantkrezil modrilom kao preporučenom metodom. Ciljevi analitičke kvalitete za hematološke brojače definirani su međunarodno prihvaćenim standardima koji obuhvaćaju sve parametre kompletne krvne slike. Po uzoru na međunarodnu procjenu IEQAS-(H) pod pokroviteljstvom SZO procjenjuju se hemoglobin (Hb), leukociti (Lkc), trombociti (Tr) i retikulociti (Rtc). Kriteriji za prihvaćanje rezultata su deklarirane vrijednosti kontrolnog uzorka unutar  $\pm 2SD$  prema primijenjenom hematološkom analizatoru i/ili ciljne vrijednosti prema veličini biološke varijacije izražene kao ukupna dozvoljena analitička pogreška. U 2005. g. u 3 ciklusa sudjelovalo je 177 laboratorija s 37 tipova brojača od 11 proizvođača. Prosječno je neprihvatljivih rezultata bilo: za Hb 2,6%, za Lkc 1,7%, za Tr 6,2% i za Rtc 22,7%. Zaključuje se kako različiti hematološki brojači zahtijevaju usklađivanje rezultata. Ne postoji ko-

ISO 15189:2003, specifically developed and released for medical laboratories, provides a unique opportunity to harmonize laboratory activity and to meet the requirements to achieve highest quality goals in all steps of the laboratory work.

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## ZR1-2

### Evaluation of results in laboratory hematology

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Department of Clinical Chemistry, Merkur University Hospital, has been involved in the International External Quality Assessment Scheme for Haematology (IEQAS - H) organized by the World Health Organization (WHO) since 1985. In 1987, it received a certificate of participation in this control scheme. Department of Clinical Chemistry has been cooperating in the external quality assessment program in laboratory hematology, which has been continuously performed in Croatia since 1988 by the Committee for External Quality Assessment Schemes under the auspices of the Croatian Society of Medical Biochemists. The objective is to show the results of the national quality control in laboratory hematology during 2005, considering the set aims of analytical quality. Commercial blood preparations are sent 3 times a year for determination of hematology parameters on counters. The sample for reticulocytes is a blood smear stained with brilliant-cresyl blue as the recommended method. The aims of analytical quality for blood counters are defined by the internationally accepted standards for all parameters of complete blood count. Modelled by the international IEQAS-H evaluation under the sponsorship of WHO, the examined parameters are: hemoglobin (Hb), leucocytes (Lkc), platelets (Plt) and reticulocytes (Rtc). The criteria for accepting the results are declared values of the control sample  $\pm 2SD$  according to the blood counter used and/or target values according to the scale of biological variation expressed as total allowed analytical error. A total of 177 laboratories participated in 3 controls conducted in 2005. The parameters of complete blood count are determined on 37 types of counters from 11 different manufacturers. Average unacceptable results: Hb 2.6%, Lkc 1.7%, Plt 6.2% and Rtc 22.7%. It is concluded that different hematology

mercijalni kontrolni uzorak idealno primjenjiv na svim hematološkim brojačima. Stoga dozvoljene granice odstupanja, koje ostvaruje većina laboratorija, ne smiju biti cilj postizanja kvalitete u redovnom radu. Na brojane Rtc utiče niz čimbenika, ali je dozvoljeno odstupanje od  $\pm 50\%$  neprihvatljivo u svakodnevnom radu. Stoga je nužno provođenje unutarnje kontrole kvalitete rada, te ispravci na analitičkom sustavu. U vanjskoj procjeni treba težiti ka što boljim rezultatima, a ispitati uzroke loših rezultata. Možda se mogu postaviti zahtjevi za bolju opremu ili dodatnu izobrazbu.

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### ZR1-3

## Procjena rezultata u laboratorijskoj koagulaciji

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Program harmonizacije laboratorijskih nalaza koji omogućuje racionalnu primjenu i pravilnu procjenu rezultata citira referentni interval za aktivirano parcijalno trombooplastinsko vrijeme (APTV) samo kao omjer. To je jedini usporedivi način izražavanja rezultata. Rezultati za APTV kroz 2005. godinu upućuju na djelomično pridržavanje preporuka, te se nameće hitna potreba za ujednačenim načinom izražavanja rezultata APTV. Trajno poticanje unapređenja visoke razine kvalitete laboratorijske dijagnostike kroz primjenu standardiziranih analitičkih sustava i standardiziranih visokoosjetljivih reagensa za protrombinsko vrijeme (PV) uz uvođenje standardiziranog načina izražavanja rezultata (uvođenje PV-INR, izražavanje rezultata za PV i APTV kao omjer) osigurati će dobru osnovu za harmonizaciju laboratorijskih nalaza. Kriterij provjere analitičke kvalitete pojedinog laboratorija je procjena rezultata koagulacijskih pretraga prema ciljnim vrijednostima koje se rabe u Međunarodnoj procjeni iz koagulacije (WHO-IEQAS-Coagulation) i iznosi 15% dozvoljenog odstupanja za PV i APTV i 20% za fibrinogen. Tijekom 2005. godine sudjelovalo je 145 laboratorija. Određivanje na automatskim koagulometrima primjenjuje se u 143 laboratorija. Za određivanje PV u 93% laboratorija rabe se standardizirani visokoosjetljivi reagensi. KV% prema skupinama reagensa je <9%. Uvidom u rezultate za APTV (podijeljeni u skupine prema reagensu) uočena je

analytical systems require a system of result harmonization. There is no single commercial control sample applicable on all blood counters. The allowed limits of deviation in external evaluation, accomplished by the majority of laboratories, are too wide to be acceptable for achieving a high quality daily performance (for Rtc  $\pm 50\%$ ). Therefore, an internal quality control is required, and it assumes statistical processing of the imprecision and inaccuracy. The best possible results should be the aim during participation in the national external quality assessment scheme.

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### ZR1-3

## Evaluation of the NEQAS coagulation results

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The established program of laboratory test harmonization cites reference range for APTT as a ratio. This is the only way to overcome the wide variation of APTT results in seconds. An overview of APTT results through NEQAS in 2005 points out that APTT-ratio has not been readily accepted. Continuous promotion of high standards in laboratory performance and improvement of analytical quality as well as the use of standardized methods and highly sensitive reagents for PT along with a unique form of expressing results (PT-INR, APTT-ratio) will provide a good basis to achieve harmonization in coagulation tests. The accepted percentage deviation from group median for PT and APTT is 15% and for fibrinogen 20% (performance criteria in WHO IEQAS-Coagulation). In 2005, 145 laboratories were registered in the program. Most laboratories (n=143) use automated coagulometers. Highly sensitive thromboplastins are used in 93% of laboratories (inter-laboratory CV <9%). There is great variability (CV 10%-20%) between different groups of reagents for APTT; 70%-80% of laboratories use APTT-ratio. Fibrinogen is determined by Clauss method in 50 of 52 laboratories. Inter-laboratory CV for normal and low concentration is <10% and 11%, respectively. Chromogenic method is used in 18 of 20 laboratories (CV 12.2%). The use of standardized methods for PT and fibrinogen and highly sensitive reagents for PT has reduced the inter-laboratory CV.

značajna varjabilnost (KV 10%-20%). Rezultate izražene u omjeru rabi 70%-80% laboratorija. Fibrinogen se određuje metodom po Claussu u 50 od ukupno 52 laboratorija. KV% za izrazito potološko područje je 11%, a za normalno <10%. ATIII se određuje preporučenom kromogenom metodom u 18 od 20 laboratorija (KV 12,2%). Rezultati za PV i fibrinogen potvrđuju da se primjenom visokoosjetljivih reagensa i preporučenih metoda smanjuje varijabilnost i omogućuje usporedivost laboratorijskih nalaza. Rezultati za APTV ukazuju na nužnost uvođenja APTV-omjera radi ujednačenog i usporedivog izražavanja rezultata.

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#### ZR1-4

### Procjena rezultata u rutinskoj analizi mokraće

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Kvalitativna analiza mokraće kao opća medicinsko-biokemijska pretraga izvodi se na svim razinama zdravstvene skrbi. Nacionalni program vanjske procjene kvalitete rada je 1997.godine zbog toga proširen i na kvalitativnu analizu mokraće kroz suradnju Hrvatskoga društva medicinskih biokemičara i Zavoda za kliničku kemiju, KB Merkur, Zagreb, potvrđenog prema standardu ISO 9001:2000. U 2005./2006. godini su provedena po 2 ciklusa kemijske analize test trakom i morfološke analize mokraćnog sedimenta. Kemijska analiza mokraće test trakom izvodi se za glukozu, bilirubin, ketone relativnu volumnu masu, pH, eritrocite, proteine, urobilinogene, nitrite i leukocite u normalnom i patološkom području. Rabi se 8-11 vrsta traka; 40% laboratorija očitavanja izvode instrumentalno. Rezultati se obrađuju prema vrsti trake i načinu očitavanja; 95%-98% rezultata je bilo prihvatljivih kod instrumentalnog, a 92%-95% kod vizualnog očitavanja. Unatoč različite osjetljivosti traka, kao i širokog raspona deklariranih vrijednosti kontrolnih uzoraka vidljivo je da instrumentalno očitavanje standardizira uvjete reakcije. Morfološka analiza mokraćnog sedimenta se izvodi pomoću 4 slike u boji sedimenta mokraće priređenih sukladno preporučenim metodama i harmonizaciji pretraga iz opće medicinske biokemije Hrvatske komore medicinskih biokemičara. U 2005. u 2 ciklusa prihvatljivi rezultati su bili za makrofage 18%, sluz 45%, granulirani cilindar 51%, bubrežni tubularni epitel 60%, hijalini cilindar 81%, gljivice 94%, pločasti epitel 98% i eritrocite 100%. U cilju bolje kvalitete slika

There is an urgent need to reach concordance and comparability in expressing APTT results.

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#### ZR1-4

### Evaluation of results in qualitative urinalysis

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Qualitative urinalysis is a test performed at each level of medical care. Therefore, in 1997 the national external quality control program was extended to qualitative urinalysis through collaboration of the Croatian Society of Medical Biochemists and Department of Clinical Chemistry, Merkur University Hospital, Zagreb, certified to the ISO 9001:2000 standard. In 2005/2006, two surveys of chemical analysis using a test strip and morphological analysis of urinary sediment were performed. Chemical analysis is based on the determination of: bilirubin, ketones, relative volume mass, pH, erythrocytes, proteins, urobilinogen, nitrites and leukocytes in normal and abnormal ranges. Eight to eleven different test strips are in use; 40% of laboratories use instrumental measuring. Results were analyzed according to the type of test strip and way of reading, and showed 95%-98% and 92%-95% of results to fall within the acceptable range by instrumental and visual measuring, respectively. In spite of varying sensitivity of different test strips and a wide range of control values, instrumental measuring has standardized the conditions of reaction. Morphological analysis of urine sediment is based on 4 color pictures following the recommendations and harmonization of laboratory tests in general medical biochemistry by the Croatian Chamber of Medical Biochemists. In 2005, there were two surveys, and acceptable results were obtained for the following analytes: macrophages 18%, mucus 45%, granular cast 51%, renal tubular cells 60%, hyaline cast 81%, yeasts 94%,

uveden je prikaz na CD, jer se virtualnom analizom slike postiže bolja vidljivost prikazanog elementa.

Svaki laboratorij dobiva ukupne rezultate uz naznaku vlastitih rezultata. S obzirom na kliničku vrijednost analize sedimenta mokraće, naročito u hitnoj laboratorijskoj dijagnostici, smanjenje broja grješaka se postiže primjenom preporučenog postupka supravitalnog bojanja sedimenta mokraće, dok se dodatnom izobrazbom poboljšava prepoznavanje svih elemenata mokraćnog sedimenta u cilju stalnog poboljšanja kvalitete rutinske analize mokraće.

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## ZR1-5

### Procjena rezultata specijalističkih biokemijskih pretraga – pH i plinovi u krvi

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Program vanjske procjene kvalitete rada medicinsko biokemijskih laboratorija (MBL) koji provodi Hrvatsko društvo medicinskih biokemičara u suradnji sa Zavodom za kliničku kemiju KB Merkur, certificiranom prema standardu ISO 9001:2000, proširen je na analizu pH i plinova u krvi od 2003. godine, s obzirom na to da se ovaj dio specijalističke laboratorijske dijagnostike provodi u velikom broju MBL na svim razinama zdravstvene skrbi. Vanjska procjena kvalitete pH i plinova u krvi provodi se tri puta na godinu analizom jednog komercijalnog kontrolnog uzorka, koji je puferirana vodena otopina bikarbonata ekvilibrirana s točno poznatom razinom O<sub>2</sub>, CO<sub>2</sub> i N<sub>2</sub>. pH i plinovi u krvi određuju se u 42 MBL na acidobaznim analizatorima različitih proizvođača uključujući Bayer Diagnostics (68%), Nova Biomedical (12%), Instrumentation Laboratories (7%), Radiometer (5%). Rezultati pojedinih laboratorija za pH, pCO<sub>2</sub> i pO<sub>2</sub> grupiraju se prema metodama i procjenjuju u odnosu na ciljne vrijednosti koje označavaju ukupnu dozvoljenu analitičku pogrešku i/ili deklarirane vrijednosti proizvođača komercijalnog kontrolnog uzorka prema metodi određivanja. Procjena rezultata mjerenja pH pokazala je nisku varijabilnost (KV%) unutar metode koja je definirana proizvođačem acidobaznog analizatora (acidosa: 0,05%-0,31%, normalno područje: 0,14%-0,24%, alkaloz: 0,04%-0,45%) i visoku razinu kvalitete uz 97%-100% prihvatljivih rezultata (±0,06 od srednje vrijednosti primijenjene metode). Rezultati za pCO<sub>2</sub> su pokazali da ciljeve

squamous cells 98%, and erythrocytes 100%. In order to achieve better quality of pictures, presentation on CD has been introduced for better visibility because virtual picture analysis yields better element identification. Each laboratory receives overall results, its own results being specially marked. In the light of the clinical relevance of urinalysis, especially in laboratory diagnosis at emergency units, a reduced rate of errors has been achieved by using standardized procedures for urine sediment and by continuing education in sediment element identification in order to permanently improve the quality of routine urinalysis.

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## ZR1-5

### Evaluation of specialist biochemistry test results – pH and blood gas analysis

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External quality assessment in medical biochemistry laboratories (MBL), which is performed by the Croatian Society of Medical Biochemists in collaboration with Department of Clinical Chemistry, Merkur University Hospital, certified to the ISO 9001:2000 standard, since 2003 has included acid base analysis because this part of specialist laboratory diagnosis is performed in a large number of MBLs at all levels of health care. External quality assessment in acid base analysis is performed three times a year by analysis of one commercial control sample of the buffered bicarbonate aqueous solution equilibrated with a predetermined level of O<sub>2</sub>, CO<sub>2</sub> and N<sub>2</sub>. Blood gas analyses are performed in 42 MBLs on instruments from different manufacturers including Bayer Diagnostics (68%), Nova Biomedical (12%), Instrumentation Laboratories (7%), and Radiometer (5%). Results from particular laboratories for pH, pCO<sub>2</sub> and pO<sub>2</sub> are grouped according to methods and assessed according to the quality specifications representing the goals for total analytical error and/or acceptable range according to the manufacturer's recommendation. pH results showed a low between instrument variability, expressed as coefficient of variation (CV): 0.05%-0.31% in acidosis, 0.14%-0.24% at normal level, 0.04%-0.45% in alkalosis, and high level of quality: 97%-100% of results were satisfactory (±0.06 from the mean of the methods). Results for pCO<sub>2</sub> were within the quality criteria (±12%) for 93%-98% of MBLs. Between in-

analitičke kvalitete ( $\pm 12\%$ ) zadovoljava 93%-98% MBL. Varijabilnost rezultata unutar metode kretala se od 1,2%-5,5% kod visoke, 4,0%-7,1% kod normalne i 0,4%-7,0% kod niske razine  $p\text{CO}_2$ . Rezultati mjerenja  $p\text{O}_2$  u odnosu na zadane ciljeve analitičke kvalitete koji iznose  $\pm 1,6$  kPa ( $p\text{O}_2 < 13,3$  kPa) i  $\pm 12\%$  ( $p\text{O}_2 > 13,3$  kPa) bili su prihvatljivi u 88%-98% MBL. Varijabilnost rezultata  $p\text{O}_2$  unutar metode kretala se od 1,5%-4,8% kod visoke, 1,5%-7,0% kod normalne i 5,3%-16,0% kod niske razine  $p\text{O}_2$ , što se može objasniti matriksom komercijalnih kontrolnih uzoraka koji su pufirane vodene otopine i slabije otapaju plinove od svježih humanih uzoraka. Dobiveni rezultati ukazuju na visoku razinu kvalitete rada MBL u ovom području laboratorijske dijagnostike, što je osobito važno jer se radi o pretragama najviše kategorije hitnosti.

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## ZR1-6

### Rezultati vanjske procjene kvalitete za HbA1c

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Laboratorijsko određivanje hemoglobina A1c (HbA1c) u Hrvatskoj prisutno je već gotovo 30 godina. Tijekom tog razdoblja uvodile su se i rigorozno evaluirane različite analitičke metode, u skladu s globalnim razvojem područja. Međutim, na nacionalnoj razini je izostala odgovarajuća potpora struke u smislu praćenja i unaprjeđenja kvalitete, te osiguranja uvjeta za primjenu međunarodnih standarda. Rezultati istraživanja provedenog početkom 2005. g. pokazali su slabu dostupnost testa na području Hrvatske (radi se u samo 27 laboratorija), te šesterostruko manji broj određivanja u odnosu na preporučene potrebe za postojeću dijabetičnu populaciju. Metodologija je danas razmjerno ujednačena, s imunoturbidimetrijskim metodama zastupljenim u čak 92% laboratorija, ali postoji velik rasap u referentnim vrijednostima, koje su se kretale u rasponu od <5.7% do <7%. Također je zabrinjavajući podatak da se u 4 (15%) laboratorija rezultati izdaju u obliku ekvivalenata IFCC. Sudionici istraživanja iskazali su gotovo jednoglasno zanimanje za sudjelovanje u programu vanjske procjene kvalitete. Koncem 2005. pokrenut je nacionalni program vanjske procjene kvalitete HbA1c, i to kao modul 9 programa vanjske procjene kakvoće rada MBL koji se provodi

instrument variability of the results ranged between 1.2% and 5.5% at high, 4.0% and 7.1% at normal, and 0.4% and 7.0% at low level of  $p\text{CO}_2$ . In 88%-98% of MBLs, results for  $p\text{O}_2$  were within the quality criteria from  $\pm 1.6$  kPa ( $p\text{O}_2 < 13.3$  kPa) and  $\pm 12\%$  ( $p\text{O}_2 > 13.3$  kPa). Between instrument variability of the results was 1.5%-4.8% at high, 1.5%-7.0% at normal, and 5.3%-16.0% at low level of  $p\text{O}_2$ , which may be explained by the matrix of the control samples; aqueous based materials have poor buffer capacity and poor ability to dissolve gases compared with fresh whole blood. The results obtained pointed to the high quality of medical biochemistry laboratories in this part of laboratory diagnosis, which is very important because acid base analysis is among the analytes of the first category emergency.

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## ZR1-6

### Results of External Quality Assessment for HbA1c

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Laboratory determination of hemoglobin A1c (HbA1c) has been present in Croatia for almost 30 years. During this period, various analytical methods have been introduced and rigorously evaluated in keeping with global advancement in the field. However, appropriate professional support has failed at the national level in terms of monitoring and promoting quality and provision of conditions for the application of international standards. Results of a study conducted at the beginning of 2005 demonstrated poor test availability in Croatia (it is performed in only 27 laboratories), and six times lower number of determinations compared to the recommended requirements for the existing diabetic population. The methodology is presently rather uniform, with immunoturbidimetric methods applied in as many as 92% of laboratories, but there is a large dispersion of reference values that ranged from <5.7% to <7%. Also, it is rather inconvenient that in four (15%) laboratories results are reported in the form of IFCC equivalents. Study participants almost unanimously expressed their interest in taking part in the external quality control program which, however, had not yet been launched at the time of the survey. At the end of

u okviru HDMB. Prikazati će se rezultati preliminarnih triju ciklusa i raspraviti dometi i budući razvoj programa u svjetlu globalnog projekta harmonizacije HbA1c.

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## **ZR2 - Edukacija medicinskih biokemičara: Harmonizacija s temeljnim načelima Bolonjske deklaracije, ZR2-1**

### **Nova koncepcija diplomskog Studija medicinske biokemije – magistar medicinske biokemije: stručnjak za 21. stoljeće**

Žanić-Grubišić Tihana

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Nova koncepcija diplomskog Studija medicinske biokemije posebnu važnost daje multidisciplinskom značaju struke, pa su bitni elementi postojećeg programa Studija posebno prošireni kliničkim znanjima kako bi se osigurali temelji za kvalitetnu primjenu znanstvenih spoznaja u kliničkom okruženju. Suvremena medicina sve veću pozornost poklanja razumijevanju dinamičkih promjena u fiziologiji i metabolizmu, osobito na molekularnoj razini, te zbog toga značajno ovisi o kvalitetnoj medicinsko biokemijskoj dijagnostici. Program je usklađen s preporukama koje su prihvaćene u većini europskih zemelja za rad u medicinsko biokemijskim laboratorijima, a predviđa jedan petogodišnji ciklus izobrazbe koji završava naslovom magistra medicinske biokemije. Multidisciplinarnost se postiže tako da se kroz studij stječu: 1. temeljna znanja (matematika, kemija, fizika, statistika, biokemija, biologija, molekularna biologija), 2. biomedicinska znanja (anatomija, fiziologija, patofiziologija, histologija i citologija, imunologija, genetika, mikrobiologija i parazitologija, farmakologija), 3. stručna medicinsko biokemijska znanja (klinička biokemija, hematologija s koagulacijom, klinička imunologija, transfuziologija, klinička citologija, mikrobiologija, analitička toksikologija, molekularna dijagnostika, laboratorijska dijagnostika hitnih stanja, dijagnostika uz bolesničku postelju, racionalna laboratorijska dijagnostika itd.) te 4. znanja i vještine iz komunikacijskih disciplina, laboratorijskog upravljanja, automatizacije, elektroničke

2005, a national program for the external quality assessment for HbA1c was initiated as Modul 9 of the External Quality Assessment Program for Medical Biochemistry Laboratories, performed within the Croatian Society of Medical Biochemistry. Results of the three preliminary trials will be presented, and the scope as well as future development of the program with regard to the global HbA1c harmonization project will be discussed.

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## **ZR2 - Education of medical biochemists: Compliance to fundamental principles of Bologna declaration, ZR2-1**

### **A new concept of university degree in Medical Biochemistry – Master in Medical Biochemistry: competent expert for the 21<sup>st</sup> century**

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The new concept of university degree in Medical Biochemistry is particularly emphasizing the multidisciplinary character of the profession building it upon the long-established Medical Biochemistry degree and by elaborating the application of scientific knowledge in the clinical context. Modern medicine places an increasing emphasis on the understanding of the dynamic human physiology and metabolism at the molecular level; therefore it depends on a reliable medical biochemistry diagnosis.

The curriculum is harmonized with the recommendations accepted in the majority of European countries, and consists of an integral five-year program providing the degree of Master in Medical Biochemistry. The multidisciplinary approach is achieved by introducing various disciplines into the curriculum: 1) fundamental natural sciences (mathematics, chemistry, physics, statistics, biochemistry, biology, molecular biology); 2) biomedical disciplines (anatomy, physiology, pathophysiology, histology, cytology, immunology, genetics, microbiology and parasitology, pharmacology, etc.); 3) professional medical biochemistry disciplines (clinical biochemistry, hematology, coagulation, clinical immunology, transfusion medicine, clinical cytology, analytical toxicology, molecular diagnosis, point of care diagnosis, evidence-based medicine, etc.); and knowledge, competences and skills in communication, laboratory management,

obrade podataka, organizacije i upravljanja medicinsko biokemijskim laboratorijem, te informatizacije laboratorijskog sustava. U ukupnom petogodišnjem studiju ima 28% temeljnih, 12% biomedicinskih, 45% stručnih i 15% izbornih predmeta. Program predviđa maksimalno povezivanje osnovnih i stručnih predmeta, a stručna praksa će se provoditi već od prve nastavne godine. Predmeti su ocijenjeni prema sustavu ECTS, tako da student može dio studija obaviti i na nekom drugom sveučilištu. Nastavni plan će se izvoditi u suradnji s kliničkim bazama Fakulteta, KBC Zagreb, KB Sestre milosrdnice i KB Dubrava. To se poglavito odnosi na stručnu praksu i veliki Integrirani kolegij laboratorijske dijagnostike koji će se u trajanju cijelog 9. semestra organizirati u kliničkim laboratorijima. Novi program studija omogućava diplomiranom stručnjaku da stekne cjelovito znanje iz svih aspekata medicinsko biokemijske znanosti koje je nužno za struku i kompetencije da organizira rad i primijeni suvremene tehnologije u laboratorijsku praksu, da kompetentno tumači laboratorijske nalaze, što ga čini bitnim članom stručnog medicinskog tima koji zbrinjava bolesnika ili članom tima koji razvija i istražuje nove znanstvene spoznaje. Suvremeno obrazovanje medicinskih biokemičara s dosta znanja iz citologije, mikrobiologije, imunologije i transfuziologije omogućuje mu da može uspješno zadovoljiti trendove u struci koji su usmjereni prema sveobuhvatnim laboratorijskim znanostima, kako je to predviđeno u medicinskoj biokemiji i laboratorijskoj medicini.

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## ZR2-2

### Poslijediplomski studiji na Farmaceutsko-biokemijskom fakultetu

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Doktorski studij Farmaceutsko-biokemijske znanosti je sveučilišni poslijediplomski znanstveni studij čijim se završetkom i obranom doktorske disertacije stječe akademski stupanj doktora znanosti, znanstveno područje Biomedicina i zdravstvo. Doktorski studij traje 3-4 godine za redovne i 6-8 godina za izvanredne studente, tijekom kojih je potrebno postići minimalno 180 ECTS (*European Credit Transfer System*) bodova. Doktorski studij organizira se u dva modula: Farmaceutske znanosti i Medicinsko-bi-

automation, electronic data processing, organization and management of medical biochemistry laboratory, and information of laboratory systems. The relative proportion of the subjects is as follows: 28% of fundamental natural sciences, 12% of biomedical, 45% of professional and 15% of elective subjects.

The fundamental and professional subjects would be intensively correlated, and training in the hospital laboratory will start already from the first year. The ECTS credits will be assigned to each subject, and student mobility would be encouraged. There will be tight cooperation with the teaching hospitals connected with School of Pharmacy and Biochemistry, Zagreb University Hospital Center, Sestre milosrdnice University Hospital and Dubrava University Hospital, in particular for the course Integral Laboratory Diagnosis in the 9<sup>th</sup> semester and professional laboratory practice. At completion of the new Medical Biochemistry curriculum, the graduate would have a thorough knowledge of all aspects of medical biochemistry laboratory science relevant to the discipline and competences to organize work and apply current techniques in laboratory practice, to make interpretation of the diagnostic data and to function as a consultant in medical team, or to pursue a career in the fundamental and applied scientific research. The new concept comprises relevant knowledge in clinical cytology, microbiology, clinical immunology, transfusion medicine, analytical toxicology and molecular diagnosis, thus concurring with the current trends in Medical Biochemistry and Laboratory Medicine.

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## ZR2-2

### Postgraduate studies at School of Pharmacy and Biochemistry

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Doctoral studies in Pharmaceutical-Biochemical Sciences are university postgraduate scientific studies which, upon completion and defense of doctoral dissertation, lead to the degree of Doctor of Science, scientific field Biomedicine and Health. Doctoral study takes 3-4 years for full-time and 6-8 years for part-time students, during which time a minimum of 180 ECTS credits have to be earned.

Doctoral study in Pharmaceutical-Biochemical Sciences at School of Pharmacy and Biochemistry, University of



okemijske znanosti. Namijenjen je farmaceutima, medicinskim biokemičarima te drugim stručnjacima iz znanstvenoga područja Biomedicine i zdravstva i područja Prirodnih znanosti. Program doktorskog studija načelno je usporediv s europskim programima (i šire) ili dijelovima programa doktorskih studija područja biomedicine i prirodnih znanosti, kao i različitih integriranih programa drugih doktorskih studija. Temelji se na kompetitivnim znanstvenim istraživanjima te obrazuje znanstvenike sa specifičnim stručnim znanjima neophodnima za prevenciju, otkrivanje, dijagnostiku i praćenje bolesti te oblikovanje i primjenu učinkovite terapije za specifičnu bolest. U tom smislu u skladu je s odgovarajućim nacionalnim prioritetima. Studij uključuje A) organiziranu nastavu (obvezne, modularne, metodološke i izborne predmete) i B) aktivno bavljenje znanstveno-istraživačkim radom, a završava polaganjem ispita, pozitivnom procjenom znanstvene aktivnosti, pozitivnom ocjenom i obranom doktorskog rada.

### 1. godina studija

A – temeljni predmeti (4 ECTS); modularni predmeti (6 ECTS); metodološki predmeti (4 ECTS); izborni predmeti (8 ECTS)

B – znanstvena aktivnost (38 ECTS)

### 2. godina studija

A – modularni predmeti (4 ECTS); izborni predmeti (10 ECTS);

B – znanstvena aktivnost (46 ECTS)

### 3. godina studija

B – znanstvena aktivnost (60 ECTS)

Farmaceutsko-biokemijski fakultet organizira i poslijediplomsku nastavu od godine dana u okviru 4 odobrena programa specijalizacija u sustavu zdravstva (Medicinska biokemija, Analitička toksikologija, Analitika i kontrola lijekova i Farmaceutska tehnologija). U tijeku je također izrada prijedloga programa za još 4 poslijediplomska specijalistička studija u trajanju od jedne godine.

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Zagreb, is organized in two modules: Pharmaceutical Sciences and Medical-Biochemical Sciences. The program is intended for pharmacists, medical biochemists and other professionals in the field of Biomedicine and Health and the field of Natural Sciences. The study *curriculum* proposed is, in principle, comparable with European *curricula* or parts of doctoral study *curricula* in the field of biomedicine and natural sciences as well as different integrated *curricula* of other doctoral studies. The study is based on competitive scientific research and educates scientists in acquiring specific competences indispensable for the prevention, detection, diagnosis and monitoring of diseases as well as for designing and application of efficient therapies. In this respect, the *curriculum* complies with the relevant national priorities. The study comprises: (A) organized instruction (basic, modular, methodological and elective courses), and (B) active engagement in scientific research; and is ended by taking an exam, favorable evaluation of research activities, passing grade and defense of doctoral dissertation.

### 1<sup>st</sup> year

A – basic courses (4 ECTS credits); modular courses (6 ECTS credits); methodological courses (ECTS credits); elective courses (8 ECTS credits)

B – research activity (38 ECTS credits)

### 2<sup>nd</sup> year

A – modular courses (4 ECTS credits); elective courses (10 ECTS credits)

B – research activity (46 ECTS credits)

### 3<sup>rd</sup> year

B – research activity (60 ECTS credits)

School of Pharmacy and Biochemistry also organizes one-year postgraduate courses within 4 approved programs of specialist training in the health system (Medical Biochemistry, Analytical Toxicology, Analytics and Drug Control, and Pharmaceutical Technology). Also, under way is making the proposal of the *curricula* for another four postgraduate specialist studies, each taking one year.

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## ZR2-3

**Međunarodna suradnja u izobrazbi medicinskih biokemičara**

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U cilju prilagodbe visokim standardima obrazovanja u Europskoj Uniji, u skladu s Bolonjskim procesom i potrebama razvoja struke, Farmaceutsko-biokemijski fakultet je neprestano poduzimao niz mjera u reformi nastavnog procesa, koje su kroz uvođenje većeg broja izbornih predmeta, podučavanje i usvajanje znanja utemeljenog na rješavanju problema, te mobilnosti studenata omogućile bolje profiliranje studenata i njihovu bolju izobrazbu. Dobar uvod u ove promjene bilo je potpisivanje sporazuma Republike Hrvatske s drugim zemljama u centralnoj i istočnoj Europi radi promicanja suradnje na području visokoškolskog obrazovanja u okviru projekata CEEPUS (*Central European Exchange of Programs of University Studies*). Suradnja se u okviru visokoškolskog obrazovanja ostvaruje kao razmjena studenata i profesora između srodnih fakulteta koji su udruženi u projektu. Studenti registrirani na jednom od fakulteta u mreži mogu dobivati novčanu potporu za studiranje u inozemstvu ne samo na dodiplomskom nego i na poslijediplomskom ili doktorskom studiju, a vrijeme provedeno u studiranju vani, koje je srodno našem programu studija, priznaje se kao dio studiranja na matičnom fakultetu. Zavod za medicinsku biokemiju i hematologiju je od 1996. godine koordinator projekta CEEPUS s jedanaest partnera, a to su zavodi za kliničku biokemiju ili zavodi za biokemiju farmaceutskih i medicinskih fakulteta u zemljama srednje i istočne Europe. U okviru toga projekta studenti medicinske biokemije proveli su u inozemstvu od jednog do tri mjeseca slušajući predavanja, radeći eksperimentalno na temi diplomskog rada ili obavljajući obveznu ljetnu praksu kao dio nastavnih obveza. U okviru projekta CEEPUS Fakultet u suradnji sa studentskom udrugom svake godine organizira ljetne škole na odabranu temu koja se obrađuje s kliničkog, dijagnostičkog i terapijskog aspekta, uz sudjelovanje studenata medicinske biokemije, farmacije, medicine i stomatologije. Time se postiže bolje obrazovanje stručnjaka za sve zahtjevniju suvremenu praksu u sustavu zdravstvene zaštite.

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## ZR2-3

**International collaboration in the education of medical biochemists**

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With respect to the current changes in the national system of high education, aimed at satisfying the high educational standards of the European Union in compliance with the Bologna process and the development of the profession, the Zagreb University School of Pharmacy and Biochemistry has undertaken a series of measures to reform the teaching process. Changes including the introduction of a larger number of elective subjects, problem-based teaching and learning (PBL), and obligatory mobility of the students will enable their better profiling and training for modern professional and research challenges. Good introduction in this manner was made in 1996, when Republic of Croatia signed agreement with other Central and Eastern European countries in promoting cooperation in the field of high education within the framework of the Central European Exchange Programme for University Studies (CEEPUS). Cooperation in the field of high education between the contracting parties has been realized through particular inter-university cooperation and mobility of students and teaching staff. Students registered at universities are eligible for support within the CEEPUS program, up to and including doctoral or postgraduate level, provided that the period of study or training at the host university, which is compatible with the *curriculum* at the student's home university, forms part of his or her university studies. Since 1996, Department of Medical Biochemistry and Hematology, School of Pharmacy and Biochemistry, has been coordinator of the CEEPUS project with eleven partner universities from Central and Eastern European countries. In the frame of this project, students of medical biochemistry used to spend one to three months abroad during their study period. Attending the lectures, working on diploma thesis or obligatory summer practice were the main types of instructions in the frame of the project for them. Each year, Zagreb School of Pharmacy and Biochemistry has organized summer school in the frame of the project, based on multidisciplinary approach to a selected topic, with international participation of professors and students of medical biochemistry, pharmacy, medicine and dental medicine. Achievements of this project have mainly been observed in better education of medical biochemists for the needs of the increasingly demanding modern practice within the health care system.

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**ZR2-4****Kako uskladiti edukaciju s potrebama medicinsko biokemijske struke?**

Dodig Slavica

Dječja bolnica Srebrnjak, Zagreb, Hrvatska

Brz napredak medicinskih znanosti te razvoj novih dijagnostičkih postupaka uvjetovao je da se medicinski biokemičari tome napretku moraju trajno prilagođavati, a nove spoznaje ugrađivati u temeljna znanja stečena u dodiplomskoj izobrazbi. U tijeku studija Medicinske biokemije na Farmaceutsko biokemijskom fakultetu medicinski biokemičar stječe temelje za razna područja: biokemijska, hematološka, molekularno biološka i kemijska istraživanja u biološkom materijalu u svrhu utvrđivanja uzroka bolesti, održavanja zdravlja, prevencije bolesti i praćenja uspjeha liječenja. Daljnje usavršavanje medicinskog biokemičara trajan je proces, koji se odvija na poslijediplomskom studiju i specijalizaciji, te sudjelovanjem na stručnim predavanjima, tečajevima trajne izobrazbe, kongresima iz područja medicinske biokemije, ali i iz područja medicine (ovisno o kategoriji zdravstvene ustanove u kojoj je medicinski biokemičar zaposlen, subspecijalizacija u području kojim se zdravstvena ustanova bavi). U ovoj će se radionici raspravljati o osposobljenosti medicinskog biokemičara za današnje potrebe struke.

*E-mail: slavica.dodig@zg.t-com.hr***ZR2-4****How to harmonize education and requirements of the medical biochemistry profession?**

Dodig Slavica

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Since modern clinical chemistry is changing rapidly as new medical knowledge and technologies become available, a competent medical biochemist must be able to synthesize and implement both graduate and postgraduate skills and knowledge. The study of Medical Biochemistry at School of Pharmacy and Biochemistry, University of Zagreb, is designed to provide a medical biochemist with the basic skills needed for a career in clinical biochemistry (biochemistry, hematology, molecular and chemistry investigations) within the frame of health service: detection of the cause of disease, health maintenance, disease prevention, and therapy monitoring. Medical biochemist requires continuing education to maintain his professional skills. Much of this is done by postgraduate study and specialization; and through professional meetings, courses of continuing education in the field of both clinical chemistry and medicine (depending on the health care institution where the medical biochemist is employed, "in house" subspecialization). In this workshop, participants will discuss the qualifications of medical biochemist for contemporary professional requirements.

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**ZR3 - D-dimeri: Definicija, primjena u klinici, standardizacija i harmonizacija metoda, ZR3-1****Definicija i pregled dostupnih metodologija za kvantitativno određivanje D-dimera**

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Prema definiciji naziv D-dimer se odnosi na završni, odnosno najmanji razgradni proizvod umreženog fibrina približne molekularne mase od 190 kDa, koji nastaje fibrinolitičkim djelovanjem plazmina. Sastoji se od 2 D-domene susjednih Y-lanaca fibrinskog polimera međusobno povezanih kovalentnom vezom koja nastaje djelovanjem aktiviranog faktora zgrušavanja XIII (XIIIa) te predstavlja neoepitop specifičan za fibrin. U svim testovima za određivanje D-dimera rabe se monoklonska protutijela specifična za epitope koji se nalaze na fibrinskom fragmentu D-dimer, ali ne i na fibrinogenskom fragmentu D, drugim razgradnim proizvodima fibrinogena ili nativnom fibrinogenu. Od 1983. godine kad je opisano prvo monoklonsko protutijelo koje reagira sa specifičnim neoepitopom D-dimer, priređena su različita monoklonska protutijela te brojni specifični imunokemijski testovi za kvantitativno određivanje D-dimera. Danas je komercijalno dostupno više od 30 testova za određivanje D-dimera u kojima se rabi više od 20 različitih monoklonskih protutijela specifičnih za D-dimer. S obzirom na metodologiju, testovi za određivanje D-dimera mogu se podijeliti na: enzimi-munokemijske testove na krutom nosaču (ELISA), automatiziranu fluorescentnu metodu ELISA za pojedinačne uzorke (ELFA), imunofiltraciju (membranska ELISA), lateks imunoturbidimetrijske testove (LPIA) i imunofluorimetrijske testove. Većina ovih metodologija je automatizirana, a kao uzorak se rabi plazma ili puna krv. Testovi se međusobno razlikuju, a to se osobito odnosi na preporučeni referentni interval i graničnu vrijednost za isključivanje tromboze. Uz to, razlikuju se prema monoklonskom protutijelu i vrsti kalibratora koji se rabi u testu, te jedinicama u kojima se izražavaju rezultati (mg/L ili jedinice ekvivalentne fibrinogenu – mg FEU/L). U praksi fragment D-dimer predstavlja samo mali dio ukupnih D-dimera koji se određuje u testovima. Naime, protutijela reagiraju s razgradnim proizvodima fibrina različite molekularne mase, koji uključuju fragment D-dimer kao i visokomolekularne te niskomolekularne razgradne proizvode fibrina te intaktni fibrinski ugrušak. Zbog razlike u specifičnosti protutijela testovi se uvelike razlikuju s obzirom na osjetljivost prema razgradnim proizvodima fibrina, kao i prema utje-

**ZR3 - D-Dimers: Definition, clinical application, standardization and harmonization of methods, ZR3-1****Overview and brief description of available methodologies for quantitative determination of D-dimers**

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By strict definition, D-dimer fragment represents a stable, terminal product generated by plasmin degradation of cross-linked fibrin, with an approximate molecular weight of 190 kD. It consists of 2 covalently bound D-domains on adjacent fibrin Y chains within a fibrin polymer. All assays for the determination of D-dimer antigen are based on monoclonal antibodies that react with conformational epitopes generated by factor XIIIa-induced crosslinking on fibrin fragment D-dimer that are not present on fibrinogen fragment D, other fibrinogen degradation products or native fibrinogen. Since 1983, when a study on the first monoclonal antibody reactive with D-dimer specific neoepitope was published, various monoclonal antibodies have been prepared and a number of quantitative assays have been developed. Nowadays, more than 30 D-dimer assays, based on more than 20 different D-dimer specific monoclonal antibodies, are present on the market. According to methodology, assays can be divided into: microtiter plate ELISA assays, automated single-sample ELISA system (enzyme-linked fluorescence assay-ELFA), immunofiltration assays (membrane ELISAs), latex-enhanced photometric immunoassays (LPIA) and immunofluorometric assays. These principles have been incorporated in a variety of automated techniques that use plasma or whole blood as sample material. There are discrepancies in the comparability of various assays, particularly in terms of reference ranges and cut-off values used for the exclusion of thrombosis. The potential sources of variation among D-dimer assays include the use of a variety of different monoclonal antibodies and different commercial calibrators. Furthermore, results are reported in mg/L or as fibrinogen equivalent units (FEU). Generally, D-dimer represents only a small part of the total D-dimer antigen measured by current D-dimer antigen assays. Assays detect an array of fibrin compounds of different molecular weights, including fibrin fragment D-dimer as well as higher molecular weight fibrin degradation products, fibrin X-oligomers and intact fibrin clots. Due to differences in epitope specificity and assay performance, assays differ concerning their preference to high or low molecular weight fibrin derivatives and cross-reactivity

caju razgradnih proizvoda fibrinogena. Niti jedan test za određivanje D-dimera nije idealan. Idealan bi test morao biti jednostavan za izvođenje, brz, jeftin, kvantitativan, s velikim mjernim rasponom te dokazan u odgovarajućim kliničkim studijama.

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## ZR3-2

### D-dimeri: različite metode, različiti rezultati.

#### Iskustvo s programom vanjske procjene kvalitete

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D-dimer se sve više rabi u dijagnostici venske tromboembolije (VTE). Stoga se javila potreba za dobro kontroliranim testovima za D-dimer koji će se moći uspješno primjenjivati i izvan pažljivo kontroliranih kliničkih ispitivanja. Potrebni su potpuno kvantitativni testovi, a polu-kvantitativni testovi na osnovi lateksa na stakalcu nisu prikladni za ovu namjenu, jer su najniže razine D-dimera koje se mogu otkriti normalno više od razina D-dimera prisutnih u nekim slučajevima s potvrđenom VTE. U preglednoj studiji u okviru UK National External Quality Assessment Scheme (NEQAS, web stranica [www.ukneqasbc.org](http://www.ukneqasbc.org)) kasne 2005. godine raspodijeljen je uzorak pripremljen kao skup plazma dobivenih od osoba s povišenim D-dimerom. Medijani rezultata dobivenih različitim tehnikama (uz najmanje 10 korisnika) prikazani su na tablici, a pokazuju broj centara koji su vratili rezultate prema metodama koje rabe (za metode koje se primjenjuju u najmanje 10 centara), kao i medijan rezultata za svaku skupinu, raspon i prijelomne vrijednosti (*cut-off*) primijenjene za isključivanje DVT prema primijenjenoj tehnici.

with non-crosslinked fibrinogen and fibrin compounds. No assay is superior to the others. A perfect D-dimer assay should be simple, inexpensive, fast, quantitative, with a large measurement range, and confirmed in appropriate clinical studies.

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## ZR3-2

### D-dimers: different methods, different

#### results. The experience within an external quality assessment programme

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D-dimer is increasingly used in the diagnosis of venous thromboembolism (VTE). There is therefore a requirement for well controlled D-dimer tests which can be successfully employed outside of carefully controlled clinical trial settings. Fully quantitative assays are required and the slide based semi-quantitative latex based assays are unsuitable for this purpose because the lowest levels of D-dimer which can be detected are normally higher than the D-dimer levels present in some cases with confirmed VTE. In a UK National External Quality Assessment Scheme (NEQAS, website [www.ukneqasbc.org](http://www.ukneqasbc.org)) survey in late 2005, a sample prepared as a pool of plasmas from subjects with elevated D-dimer was distributed. The median results by different techniques (with at least 10 users) are presented below, showing the number of centres returning results according to the method used (for methods used by at least 10 centres) as well as the median of each group results, the range and the cut-offs used for DVT exclusion according to the technique in use.

Metoda / Method	n	Medijan rezultata / Median result	KV / CV	Raspon / Range	Medijan cut-off za DVT / Median cut-off for DVT	Raspon cut-off / Range of cut-offs
VIDAS (FEU)	43	990 ng/mL	12%	512–1150	500	300–1000
MDA (FEU)	24	801 ng/mL	17%	490–1040	500	300–500
Stago (FEU)	30	1030 ng/mL	8%	840–1240	500	400–2000
DB DDimer +	32	176 ng/mL	32%	96–360	192	90–500
Inst Lab	106	445 ng/mL	20%	209–700	250	130–700
MDA	17	409 ng/mL	19%	290–530	275	190–500
Trinity/ Biopool	85	288 ng/mL	13%	135–936	190	100–1000

Naši podatci pokazuju hitnu potrebu za standardizacijom testiranja i izdavanja nalaza. Kad se D-dimer rabi za isključivanje VTE, primijenjena prijelomna vrijednost (*cut-off*) mora u obzir uzeti tehniku koja se rabi za određivanje.

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### ZR3-3

## Kliničko značenje određivanja D-dimera u likvoru

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D-dimeri su specifični razgradni proizvodi umreženog fibrina. Povišene vrijednosti znak su ubrzane fibrinolitičke aktivnosti i mogu poslužiti kao specifični indeks hiperkoagulabilnosti i pojačane fibrinolize. Ranija istraživanja su pokazala da su vrijednosti D-dimera u normalnom likvoru vrlo niske ili negativne. U stanjima hipoksije ili ishemije, kada dolazi do oštećenja krvno-moždane barijere, molekule D-dimera mogu ući iz periferne cirkulacije u likvor, što rezultira povišenjem njihovih vrijednosti u likvoru. Pokazalo se, međutim, da su u stanjima akutnog subarahnoidnog krvarenja vrijednosti D-dimera u likvoru značajno više nego u krvi i opadaju s vremenom. Stoga bi određivanje D-dimera u likvoru moglo biti korisno u diferencijalnoj dijagnostici intrakranijskih krvarenja kod bolesnika s negativnim nalazom CT. Također, istraživanja su pokazala da se povišene vrijednosti D-dimera u likvoru mogu naći i kod bolesnika s malignim bolestima kod kojih postoje klinički znakovi infiltracije središnjega živčanog sustava (SŽS) malignim stanicama. Cilj ovoga rada je bio ispitati vrijednost određivanja D-dimera u likvoru kao potencijalnog biljega metastatskog procesa unutar SŽS. Isto tako, željelo se ispitati može li test poslužiti za razlikovanje patološkog intrakranijskog krvarenja od artifičijelnog krvarenja. Ukupno su analizirana 62 uzorka likvora, od toga 33 uzorka bolesnika s hematološkim malignim bolestima, 5 uzoraka likvora bolesnika s metastazama solidnih tumora, 11 uzoraka likvora sa sumnjom na krvarenje, te 13 normalnih likvora. D-dimeri su određivani automatiziranom enzim-fluorimetrijskom metodom (ELFA) na uređaju mini Vidas proizvođača bioMérieux. U svim uzorcima normalnih likvora vrijednosti D-dimera su bile <0,05 mg/L. Povišene vrijednosti D-dimera su dokazane kod 7 uzoraka likvora hematoloških bolesnika, kao i kod svih bolesnika s metastazama solidnih tumora. Od 11 uzoraka likvora koji

Our data show that there is an urgent need for standardisation of testing and reporting. When D-dimer is used to exclude VTE, the cut-off employed must take account of the technique used.

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### ZR3-3

## Diagnostic value of cerebrospinal fluid D-dimer assay

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D-dimer is a specific breakdown fragment of cross-linked fibrin, reflecting the secondary acceleration of fibrinolytic activity, and can be used as a specific index of hypercoagulability and hyperfibrinolysis. Recent investigations showed very low or negative values of D-dimers in the normal cerebrospinal fluid (CSF). Due to hypoxia and ischemia, when the function of the blood-brain barrier was damaged, these molecules were elevated in CSF. Also, the CSF D-dimer level has been reported to be significantly higher than its blood level in the acute stage of subarachnoid hemorrhage, decreasing with time. Therefore, D-dimer determination could be useful in the differential diagnosis of intracranial hemorrhage in patients with negative CT scan. Also, some investigators showed that the CSF D-dimer levels were significantly higher in neoplastic diseases with clinical evidence of the central nervous system (CNS) involvement. The aim of our study was to assess the diagnostic value of CSF D-dimer test as a potential marker of CNS involvement with neoplastic cells and carcinoma. We also wanted to assess the diagnostic value of CSF D-dimer test as a rapid method to distinguish intracranial hemorrhage from traumatic tap. D-dimer assay was performed on 63 CSF samples: 33 samples from patients with malignant hematologic diseases, 5 samples from patients with carcinoma with CNS involvement, 11 hemorrhagic samples, and 13 control samples. D-dimers were measured by the automated immunoassay system using ELFA (Enzyme Linked Fluorescent Assay) technology on a mini Vidas (bioMérieux). The levels of D-dimers were below 0.05 mg/L in all control samples. Higher levels of D-dimers were detected in 7 samples of patients with malignant hematologic diseases, and also in all 5 samples from patients with carcinoma with CNS involvement. The levels of D-dimers were higher in 9 hemorrhagic samples.

su bili krvavi, 9 ih je imalo povišene vrijednosti D-dimera. Rezultati su pokazali da određivanje D-dimera u likvoru bolesnika sa sumnjom na maligni proces može biti koristan pokazatelj infiltracije malignih stanica unutar SŽS. Na relativno malom broju uzoraka krvavih likvora test se nije pokazao dovoljno specifičnim za razlikovanje artifičnog od patološkog krvarenja, no za donošenje konačnih zaključaka test treba ispitati na znatno većem broju bolesnika.

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### ZR3-4

## Dinamičko praćenje D-dimera različitim metodama za kvantitativno određivanje

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Osnovni problem u danas dostupnim testovima za kvantitativno određivanje koncentracije D-dimera predstavlja različita specifičnost svakog pojedinog testa prema razgradnim produktima umreženog fibrina i fibrinogena. Određivanjem koncentracije D-dimera kvantitativnim testovima različite metodologije ispitivana je međuovisnost dobivenih koncentracija D-dimera i ukupnih razgradnih produkata fibrinogena i fibrina (TDP). Koncentracije D-dimera izmjerene su u plazmama 40 bolesnika pomoću NycoCard D-Dimer, IL Test D-Dimer, D-Dimer PLUS i STA Liatest D-DI, a koncentracije TDP-a pomoću testa Fibrinostika TDP. Rezultati su se razlikovali u 16/40 (40%) uzoraka koji su podijeljeni u 4 skupine prema rezultatima dobivenih NycoCard testom: I. <0,3 mg/L; II. 0,3-0,6 mg/L; III. 0,7-1,2 mg/L; IV. >1,2 mg/L. Usporedivi rezultati su dobiveni u uzorcima skupine IV. Većina rezultata je bila usporediva u skupini III, osim kod 4 negativna uzorka: 1 sa STA Liatest D-DI i 3 s IL Test D-Dimer. Najveće razlike su opažene u skupini II (9/12 uzoraka), oko granične vrijednosti za NycoCard. U 3/5 uzoraka s normalnim NycoCard vrijednostima (skupina I) dobiveni su pozitivni rezultati: 1 sa STA Liatest D-DI i 2 s D-Dimer PLUS testom. Usporednim određivanjem koncentracije D-dimera NycoCard testom i Vidas D-dimer testom dobivene su razlike u 10/48 uzoraka, a usporedbom IL Test D-dimer i Vidas D-dimer u 18/102 uzorka. Najveći broj rezultata odstupao je kod NycoCard vrijednosti <=0.3 mg/L (7/10) odnosno kod granične vrijednosti za IL test (16/102). U pojedinim uzorcima su NycoCard testom odnosno IL testom izmjerene izrazito visoke koncentracije D-dimera dok su Vidas testom dobivene

Our results suggest that the measurement of D-dimers in CSF may be useful in the diagnosis of CNS involvement with neoplastic cells. Our study failed to differentiate pathologic hemorrhage from traumatic lumbar puncture, but these results could be due to the small number of samples. Additional investigations should be performed in a greater number of samples.

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### ZR3-4

## Dynamic D-dimer monitoring by different methods for quantitative determination

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The main problems in nowadays commercially available tests for quantitative D-dimer assays are that they display variable specificity toward cross-linked fibrin derivatives as well as fibrinogen degradation products. D-dimer determination with quantitative D-dimer assays based on different methodology enabled us to investigate interdependence of D-dimer values and a correlation with total fibrinogen/fibrin degradation products (TDP). D-dimer concentrations were measured in plasma of 40 patients using NycoCard D-dimer, IL Test D-dimer, D-dimer PLUS, STA Liatest D-DI, and fibrinogen/fibrin degradation products were measured with Fibrinostika TDP. The samples were separated into four groups according to NycoCard results: I. <0.3 mg/L; II. 0.3-0.6 mg/L; III. 0.7-1.2 mg/L; IV. >1.2 mg/L. All assays gave comparable results in group IV. Majority of the results were comparable in group III, except for 4 samples that were negative: 1 with STA Liatest D-DI and 3 with IL Test D-Dimer. The greatest discrepancy between results was found in group II (9/12 samples), above the NycoCard cut-off value. At 3/5 samples with normal NycoCard values (group I) we identified 3 positive results: 1 with STA Liatest D-DI and 2 with D-dimer PLUS assay. Results obtained by comparison of D-dimer concentration with NycoCard D-dimer and Vidas D-dimer indicated differences in 10/48 samples and comparison of IL test D-dimer and Vidas D-dimer gave discrepant results in 18/102 samples. The most discrepant results were at NycoCard value <=0.3 mg/L (7/10) and above cut-off value for IL Test D-dimer (16/102). In some samples we measured a significantly higher values with NycoCard and IL Test

normalne ili tek neznatno povišene vrijednosti. U jednom od tih uzoraka dokazana je visoka koncentracija reumatoidnog faktora pa je i to jedan od čimbenika koji treba uzeti u obzir pri interpretaciji nalaza. Razlike dobivenih rezultata većinom su ipak posljedica uporabe različitih kalibratora i monoklonskih protutijela specifičnih za pojedini test, što upućuje da je neophodno bolesnika pratiti uvijek istim testom.

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#### ZR4 – Novi hematološki parametri, ZR4-3

### **Napredak u hematologiji: nedostatak željeza u svjetlu novih biokemijskih biljega i indeksa RBC (% Hypo, CHr) – Terapijski dijagram Thomas-Plot i njegova uloga u dijagnostici i terapiji**

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Nedostatak željeza (latentan ili funkcijski) kao i pojavna anemija uslijed nedostatka željeza najčešći su učinci primarne ili sekundarne nedostatne opskrbe željezom u okviru eritropoeze, kao i anemija kroničnih bolesti (ACD). Ispravna i dobro utemeljena diferencijalna dijagnoza postojećeg nedostatka željeza moguća je uz pomoć parametara kompletne krvne slike (RBC, Hgb, MCV, MCHC, MCH) te feritina. Suvremeni hematološki sustavi zasnovani na jednostaničnoj analizi pružaju dodatne morfološke podatke o kvantitativnoj konfiguraciji populacije crvenih krvnih stanica, što je osobito znakovito za nedostatak željeza. Omjer mikrocitčnih i hipokromnih eritrocita (M:H) od <0,9 opisuje postojeći nedostatak željeza uz visoku statističku značajnost, dok je hipokromija normalno dvostruko viša od mikrocytoze (usp. ovdje također i talasemija, M:H >0,9). To je suprotno oblicima funkcijskog nedostatka željeza u kombinaciji s akutnom ili kroničnom upalom, te s porastom proteina akutne faze (CRP) ili pak s ranim stadijem terapije eritropoetinom (r-hu EPO). Ovi oblici funkcijskog nedostatka željeza mogu se otkriti uz pomoć novih hematoloških parametara i objasniti u smislu diferencijalne dijagnostike, omogućavajući tako "dublju analizu malfunkcije metabolizma željeza". Parametri kompletne krvne slike su, blago rečeno, "prespori" za rano otkrivanje nedostatne opskrbe željezom tijekom eritropoeze, jer se njezine jasne promjene post-

D-dimer beside normal or almost normal D-dimer levels with D-dimer Exclusion assay. In one of those samples we proved high values of rheumatoid factor which is one of the factors that should be taken into consideration with interpretation of results. The differences of the obtained results are mostly due the usage of different calibrators and different monoclonal antibodies which suggest that the follow-up of patients should be always performed with the same assay.

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#### ZR4 – New hematological parameters, ZR4-3

### **Advances in hematology: iron deficiency states in the light of new biochemical markers and RBC indices (% Hypo, CHr) – Thomas-Plot Therapeutic Diagram and its relevance in diagnosis and therapy**

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Iron deficiency (latent or functional) as well as a manifest iron deficiency anemia are the most frequently appearing impacts of primary and secondary iron supply shortage within erythropoiesis and also in anemias of chronic diseases (ACD). A correct and well-founded differential diagnosis of an existing iron deficiency is possible with the aid of CBC parameters (RBC, Hgb, MCV, MCHC, MCH) and with ferritin. Modern hematology systems based on single cell analysis yield additional morphological information about the quantitative configuration of the red blood cell population, which is especially characteristic for iron deficiency. A ratio of microcytic and hypochromic erythrocytes (M:H) of <0.9 describes an existing iron deficiency with high statistical significance, and hypochromia is normally twice as high as microcytosis (cp. here also thalassemia, M:H >0.9). This contrasts with the forms of functional iron deficiency in combination with acute or chronic inflammation and with an increase of acute phase proteins (CRP) or in the early stage of erythropoietin therapy (r-hu EPO). These forms of functional iron deficiency can be detected with the aid of new hematology parameters and can be clarified in a the differential diagnostic way, thus enabling a "profound analysis of iron metabolism malfunctions". The parameters of CBC are, "to say the least, too slow" for the early detection of deficiency in iron supply during erythropoiesis because



aju očite tek nakon više tjedana. Funkcijski nedostatak željeza može se otkriti ranije uz pomoć hipokromnih RBC kad se prijelomna vrijednost premaši za >5%, prije negoli nastupi značajno sniženje indeksa RBC kao što su MCV, MCHC ili MCH. Nadalje, postotak hipokromnih RBC opisuje "povijest eritropoeze" tijekom proteklih 70 dana, i to bez ograničavajućeg utjecaja bioritma ili metabolizma željeza ili koeficijenta varijacije (CV) dotične metode na konačne zaključke. Funkcijski nedostatak željeza je teško dijagnosticirati kad je istodobno prisutna upala i anemija udružena s kroničnim bolestima, jer reakcija akutne faze remeti zasićenost feritinom i transferinom. Kvocijent rezultata sTfR\* i dekadni logaritam feritina, indeks feritina, koristan je pokazatelj opskrbe željezom tijekom eritropoeze. Indeks feritina, biljeg opskrbe željezom i sadržaj hemoglobina u retikulocitima (CHr), pokazatelj potreba za željezom, čine osnovu za tzv. Dijagnostički dijagram (Thomas-Plot) za definiranje nekih stanja metabolizma željeza, poglavito u bolesnika s upalnom reakcijom ili bez nje. Odlučujući parametar je ovdje C-reaktivni protein (CRP) > ili <5,0 mg/L.

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#### ZR4-1

### Procjena novih parametara u odnosu na standarde

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Godinama su automatizirani hematološki uređaji pružali podatke o crvenim krvnim stanicama (RBC): MCV, RDW, MCH. Danas pak neki instrumenti mogu točnije diferencirati i različite bijele krvne stanice (WBC), i to ne samo u slučaju normalnih stanica, nego također u mnogim nenormalnim kliničkim situacijama. Neke tehnologije poput VCS<sup>®</sup> (Volume-Conductivity-Scatter) mogu razlikovati WBC bez značajnijih morfoloških promjena u ponašanju stanica (gotovo nativno stanje), što omogućava automatiziranu morfološku analizu WBC i primjenu tih podataka u probiru na različite nenormalnosti WBC, kao u slučaju RBC. Danas izazov predstavlja primjena ovih podataka u svrhu što boljeg otkrivanja/označavanja nenormalnih stanica, kao što su nezreli granulociti, blasti, reaktivni i maligni limfociti, plazma stanice, neutrofilna displazija (hipogranularnost) itd. Čini se kako je, nakon mnogo godina, došlo vrijeme bijelih krvnih stanica.

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their explicit changes only become apparent after weeks. Functional iron deficiency can be detected earlier with the aid of hypochromic RBCs when the cut-off is exceeded by >5%, before the RBC indices such as MCV, MCHC or MCH have significantly decreased. Furthermore, the percentage of hypochromic RBCs describes the „history of erythropoiesis“ during the elapsed 70 days, without either the biorhythm or iron metabolism or coefficient of variation (CV) of the method having a limiting impact on the conclusions. Functional iron deficiency is difficult to diagnose in conjunction with inflammation and anemia stemming from chronic diseases because ferritin and transferrin saturation are impaired by the acute phase reaction. The quotient of sTfR\* result and the decade logarithm of ferritin, the ferritin index, is a useful indicator of iron supply during erythropoiesis. The ferritin index, a marker of iron supply and the hemoglobin content of reticulocytes (CHr), an indicator of iron requirements, generate the basis for the so-called Diagnostic Diagram (Thomas-Plot) to define several states of iron metabolism, especially in patients with or without inflammatory reaction. The decisive parameter here is C-reactive protein (CRP) > or <5.0 mg/L.

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#### ZR4-1

### New clinical applications with WBC automated morphological analysis

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For many years, automated hematology instruments were used to provide morphological information on red blood cells (RBC): MCV, RDW, MCH. Today, some instruments are capable of a more accurate differentiation among different white blood cells (WBC) not only when the cells are normal but also in many of abnormal clinical situations. Some technologies such as VCS<sup>®</sup> (Volume-Conductivity-Scatter) can differentiate WBCs without significant morphological changes in WBC behavior (near native state), thus permitting automated morphological analysis of WBC and use of this information in the screening of different WBC abnormalities, just as for RBCs. The challenge today is to use this information for better detection/flagging of abnormal cells, such as immature granulocytes, blasts, reactive and malignant lymphocytes, plasma cells, neutrophil dysplasia (hypogranularity), etc. It seems that now, after many years, the time has come for WBCs.

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