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E-HEALTH TOOLS FOR THE MEDICAL LAB FOR BETTER OUTCOMES

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The increased pace of digital adoption is an ally in addressing the healthcare challenges in the networked age and the provision of high quality services is a critical component of patient care, involving diagnosis, monitoring and screening services. There is little doubt that an increasing number of laboratory and healthcare tasks performed by trained professionals today will be replaced by technology. Technology tools are increasingly automating highly standardized and repetitive routine laboratory tasks while wearable technologies, connected diagnostic and monitoring tools are facilitating the delivery of care to patients. eHealth changes the traditional delivery of healthcare. The digital healthcare transformation is taking place globally, the future is connected, patient centered, mobile and social. This digital paradigm is exerting a profound impact in Lab medicine. Digital lab medicine is totally disruptive because the changes in the capabilities to integrate and visualize complex diagnostic data. This represents an opportunity for radical changes to diagnostic health strategies in the rapid changing healthcare environment. These innovations are changing the facts like how we live, how we acquire information, how we interact with each other, and how we practice the profession of specialist in lab medicine. In the face of exponential growth of applications in telemedicine, tele-biology and m-health with the smart phone applications, the laboratory systems need to meet new demands for data exchange with clinical electronic record systems for test requesting and results reporting. The scope and scale of m-health interventions range from simple direct-to-individual consumer and interactive patient provider communications to more complex computer-based systems facilitating coordinated patient care and management. Properly implemented digitization can enable better patient outcomes, improve convenience, potentially lower healthcare costs. The new tools that can give us a much more high-definition view of the patients; because the wearable sensors that track a wide range of important physiologic parameters continuously. The digitization of health care and lab medicine can also improve the clinician-medical biologist-patient relationships, allowing more time for human interaction when care is boosted by digital technologies that better individualize diagnostics and patient monitoring. The future of Lab medicine is challenging with the integration of these disruptive technologies, increasing innovation and transformational changes. The specialist in lab medicine must reinvent his leadership in face of the digital transformation, as well as reinforce strong relationships with patients and practitioners to provide always-on services. Because the plethora of existing apps, it is important to continually evaluate which apps are effective for which patients and situations. Digitalization and e-health characterize not only a technical development, but also a state of mind, a way of thinking and a commitment for networked, global thinking to improve health care locally regionally and worldwide. eHealth also presents a series of ethical and legal challenges among other things, privacy, consent and liability are implicated, as are changes in the health care professional-patient relationship. The convergence of personalized medicine with digital health and artificial intelligence, systems biology, social networks, big data analytics and precision medicine is on the cusp of enabling an emerging field: scientific wellness. By leveraging Big Data and scientific advancements while maintaining the important doctor-patient-lab specialist bond, the future of healthcare system will go beyond curing diseases. it will be possible to offer more personalized and cost-effective care systems through predictive patient analytics.

DIGITAL TOOLS IN LABORATORY MEDICINE

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The use of digital technologies and mobile health (mHealth) applications is driven by the continuous development of connected devices, sensors and digital health applications. Digital technologies participate in precision medicine with potential impact on prevention, early diagnosis and monitoring of chronic diseases. An increasing evidence shows that mHealth technologies decreases the number of disease-related health outcomes in patients suffering from chronic diseases in comparison to regular care. In the case of diabetes, significant improvements were observed in compliance with better control of glucose levels, compliance, and stress levels. Process improvements were also reported with fewer failed appointments, quicker diagnosis and treatment, and improved teaching and training. In patients with heart failure, mHealth can participate in a decrease of the length of stay in hospitals and in maintaining the activities of daily living. Digital tools have also the potential to strongly reinforce patient empowerment and engagement. The impact of mHealth is clearly evident in the increase in self-managed patients affected by chronic conditions, whereby patients with chronic conditions make day-to-day decisions about self-managing their illnesses. The efficiency of patient empowerment and self-management has been demonstrated in diabetic patients and more empowerment and interactivity stimulated by sensors and connected devices. The use of digital technologies could also increase the literacy of patients with chronic diseases. Education through mHealth technologies complements traditional patient education in supporting patients to live the best possible quality of life with their chronic condition. The educational potential is greater as it will also contribute to making the patients with chronic diseases more effective in their decisions and therefore can improve outcomes and can reduce costs. This new manner of education is also contributing to more self-management of the conditions and to a closer adherence to physicians' recommendations. Last but not least, the development and use of emerging digital technologies will rely on patient centric approaches as well as more multidisciplinary team work engaging multiple healthcare professionals and more dynamic junctions between primary care and hospitals.

MACHINE LEARNING AND LABORATORY MEDICINE

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Artificial intelligence (AI) is a field of computer science that aims to mimic human thought processes, learning capacity, and knowledge storage. Computer science advances and ultra-fast computing speeds find artificial intelligence (AI) broadly benefitting modern society-forecasting weather, recognizing faces, detecting fraud, and deciphering genomics. While diagnostic confidence never reaches 100%, combining machines plus physicians reliably enhances system performance. AI is being successfully applied for image analysis in radiology, pathology, and dermatology, in robot assisted surgery, virtual nursing assistant, administrative workflow assistant, fraud detection, dosage reduction error, connected machines, clinical trial participant identifier, preliminary diagnosis, automated image diagnosis, cybersecurity. Machine learning is a type of AI that allows computer programs to adjust when exposed to new data, in effect, »learning« without being explicitly programmed and used algorithms that identify patterns in structure data. Machine learning is similar to data mining in which databases are examined by humans to produce new information and insight. However, machine learning provides an unbiased analysis of the data. AI has the potential to generate a new revolution in laboratory medicine. Perhaps the best-known example of AI in healthcare is IBMs Watson. This has found broad utility in managing hospital care more effectively, accelerating drug discovery, identifying appropriate cancer treatments, and matching patients with clinical trial. One application relevant to the reporting of clinical laboratory results is Watson for Genomics. This AI-based system rapidly analyzes and categorizes genetic alterations related to cancer progression revealed by genetic analysis of tumor tissue and then provides potential therapeutic options. A core diagnostic modality in the clinical laboratory is the interpretation of images from body fluids or tissue. In the routine evaluation of peripheral blood and urine, automated instrumentation has been introduced. However, the examination of tissue samples (surgical pathology) has not advanced into an automated process. The emergence of combining digital whole slide imaging and artificial intelligence may lead to AI-centered diagnoses of tissue samples. The Internet of Things (IoT) refers to the wide range of devices (things) that can be connected to the Internet. In the clinical

laboratory, one prospect is the connection of all laboratory components to a system from which they can be monitored and controlled. For example, a clinical analyzer can be a member of the IoT, and its connectivity permits remote monitoring for a proactive response to instrument issues. Another example, is an IoT temperature sensor inside a specimen transport container to obtain real-time data about sample conditions (e.g., temperature) during transit and delivery. Another important AI-based technology is augmented reality, a technology that integrates digital information with a user's environment in real time. In healthcare, one application is in phlebotomy to make finding veins easier. Based on the current pace of development in AI, it seems highly likely that the clinical laboratory will make more use of AI-based technologies such as decision support systems to aid human image-based diagnosis.

LEADERSHIP SKILLS

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Besides knowledge, competence and skills in laboratory medicine, specialists in laboratory medicine are nowadays required to have a number of soft skills to help them positively interact with their employees and their team members. Being in a leadership position certainly requires good leadership skills. It is difficult to say which are the most important skills, one leader must have. Being a good leader means to excel in many of them, if not all. The more, the better. For sure, a good leader is able to communicate effectively. Communication means not only to articulate your thoughts clearly, without ambiguity and with utmost clarity, but also to be a good and active listener, who is able to read nonverbal communication and verbal language. A good leader will be the one who will always facilitate group conversations to make them as focused as possible to the meeting outcomes and goals. A good leader is also the one who is committed to the continuous and ongoing pursuit of his or her mission and vision. The most successful leaders are those who have the ability to always capitalize their efforts to turn their vision into a reality. Great leaders are trustworthy and responsible, they treat others with fairness and empathy, always showing respect towards his/her colleagues and teammates. One important skill of successful leaders is to be modest and humble about the value of themselves. Instead of viewing themselves as being great and irreplaceable, good leaders will always be encouraging others to grow. Leadership skills also involve ability to effectively delegate tasks and motivate others. To be a successful leader one must be trustworthy, creative and flexibile. Last, but not the least, great leaders must be honest and have high integrity, these values are indeed the true foundations of a good leadership. Although some would argue that leaders are born, not made, the truth is that leadership skills can be learned and developed. This lecture will provide an overview of some most important skills of a leader, show why they are important and how these skills can be obtained and improved.

PROJECT MANAGEMENT

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Laboratory diagnostics plays a crucial role in modern medicine, since it provides essential contributions to the clinical decision making, to the managed care, but also for optimizing care pathways, streamlining activities before, during and after analysis, promoting standardization and/or harmonization, and improving appropriateness. Recent changes in the essential nature of clinical laboratories, mostly resulting from technological advancements, shortage of vocations and cost-containing policies, have however contributed to catalyze a paradigmatic transformation of laboratory professionals. Original and basic tasks, mostly encompassing development or selection of analytical techniques along with organization of workflows within the laboratory, need now to be integrated and combined with a number of new responsibilities. The main drivers of this paradigm shift essentially include major commitment to information technology, internal (i.e., consolidation) and external (i.e., networking) laboratory reorganization, increasing liability to administrative skills, human resource management and budgeting, as well as the co-called »diagnostic stewardship« and the progressive integration of new diagnostics disciplines such as the »-omics« sciences along with more conventional techniques (e.g., clinical chemistry, immunochemistry, hematology, hemostasis, microbiology and virology). Importantly, laboratory professionals need now to be more familiar with project management (i.e., the practice

of achieving specific goals and meet specific targets), which not only encompasses laboratory reorganizational efforts (human, technical and economic), but also necessitates test menu optimization, elimination of manually-intensive procedures and obsolete tests, budget planning and monitoring, provision of appropriate education and training to the staff, as well as a close relationship with syndicates, hospital administrators and politicians. These new tasks would hence require that clinical expertise and technical training shall be integrated with administrative skills, thus partially transforming laboratory professionals in business people and executives, which well depict a new and more complex job description of laboratory professionals. Albeit the need to stay abreast of these newly essential activities has been somehow overlooked in the past, the time has come to move forward towards an innovative and multifaceted dimension for our discipline.

COMMUNICATION BETWEEN THE CLINICAL LABORATORY AND ITS USERS

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One definition of communication is 'the imparting or exchanging of information by speaking, writing, or using some other medium'. This concept is familiar to everyone but achieving effective two-way communication is a challenge in all areas of professional practice, including laboratory medicine. Communication between the clinical laboratory and its users occurs mainly in the pre-analytical and in the post-analytical phases of operation. These two phases account for up to 90% of all laboratory medicine errors and in most cases the errors can be attributed to a breakdown of communication. Examples of communication errors include:

Pre-analytical phase: wrong test, wrong sample, wrong container, wrong transport, inaccurate patient information;

Post analytical phase: results not received, results ignored, results miss-understood, inappropriate patient follow-up.

Optimizing communication between the clinical laboratory and its users should be a central component of all laboratory improvement plans and it is an essential element of quality management and laboratory accreditation. A systematic approach to improving communication can be developed by addressing simple questions:

Who are the users with whom I should communicate?

What is the information that needs to be communicated?

When should I communicate with these user groups?

What are the most effective communication methods for each of the user groups?

How can the effectiveness of my laboratory communication be measured?

Examples of 'good' and 'poor' answers to these questions will be presented to illustrate how simple actions can increase the effectiveness of communication. Finally, it must be remembered that effective communication is two-way, so that users must be able to have clear and easy access to the clinical laboratory for information or advice. Examples of how this may be achieved will be presented. Listening is often said to be the most important communication skill.

LABORATORY STANDARDS IN SLOVENIA: GROWING UP STEP BY STEP

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The history of Laboratory Medicine in Slovenia has begun in the fifties of the previous century, when our colleagues who have been working in the field of medical biochemistry wished for a society that would pursue better recognition of medical biochemistry in Slovenian health care and enhance its professional development and value. After several attempts, on October 2nd 1961 our colleagues of that time decided to join Slovenian Pharmaceutical Society and established Section of Medical Biochemists and acted as a part and within it. After 33 years, in 1995, the association became independent with the name of Slovenian Association of Clinical Chemistry (SZKK) and with first own statutes. Since then SZKK has been a member of the International Federation of Clinical Chemistry and Laboratory medicine (IFCC), and in mid-nineties it joined also the European

Federation of Clinical Chemistry and Laboratory Medicine (EFLM), where our members are actively involved in various working groups and committees. According to important efforts for better recognition and harmonization of our profession on EFLM level, in March 2014 we have been renamed into Slovenian Association for Clinical Chemistry and Laboratory Medicine (SZKKLM). Throughout the years, also according to the intensive activities of SZKKLM, our profession achieved noticeable progress with established and implemented internal and external verification of quality of work within clinical chemistry laboratories, procedures of analysis were unified, educational system was improved and branched, permanent education courses started for all profiles, with different level of achieved education (technicians, engineers, specialists) and Republican professional College of Clinical Chemistry and Laboratory Medicine (RSK) began to operate. Today the association connects 324 members with different educational backgrounds. More than half of them are university graduates in pharmaceutical, chemical, biological, biochemical or other biomedical professional fields. A lot of them (80) have also successfully completed the specialization in medical biochemistry at Ministry of Health and also obtain academic degree (M. Sci. or PhD). Slovenian specialists in medical biochemistry regarding the achieved equivalent standard of education since 1994 and EC4/EFLM registration, can obtain the title of European Specialist in Laboratory Medicine (EuSpLM). Members' and society common goal is to ensure a constant development of clinical chemistry and laboratory medicine in Slovenia, following international standards. With association and cooperation with other Slovenian (Slovenian Chamber of Laboratory Medicine, Faculty of Pharmacy, RSK) and foreign professional (IFCC, EFLM), scientific, research and educational institutions, we are constantly improving the education system (specialization), providing the recommendations for different laboratory fields of diagnostics and impact on general development of our profession. In cooperation and under the auspices of IFCC and EFLM, the SZKKLM regularly organizes Slovenian and international congresses of clinical chemistry and laboratory medicine, conferences on the topic of accreditation and quality in medical laboratories and by organizing regular professional meetings, seminars and workshops, ensure continuing professional education of all our members (technicians, engineers and specialists). In an effort to improve the quality of work in medical laboratories on different levels (primary, secondary and tertiary level), including the private small POCT laboratories in physician's ambulant/outpatient treatment units, in 2004 we prepared and implemented, together with the authorities (Ministry of health, RSK), the By-law of Rules on minimum conditions to be met by the laboratory to obtain a work permit. With this document, which was prepared according to the ISO 15189, we established the »pre-accreditation« system, according to which each laboratory in Slovenia was expected to work. Different commissions, constituted by Medical biochemistry professionals and appointed by the Ministry of Health, every 5 years evaluate the implementation of this document in each laboratory and confirm or decline the success of the implementation according to which the Ministry of health give the permission to work. With the help of this established system, during these years we have been able to rise up the quality of the professional work in medical and POCT laboratories on a high and for the patient's safe level. Since the last three years, after establishing the national accreditation body in Slovenia (Slovenian Accreditation), we are also dealing with the more intensive approach to established accreditation process also for medical laboratories. Since now, we have already 3 national laboratories that joined pilot project and gained Accreditation according to the SIST EN ISO 15189:2013. The main problem and the reason, that accreditation process was not in the past and is still not so intensive, is the really high financial cost, that should be needed for its implementation. In an effort, to increase the visibility of our profession, in 2014 SZKKLM for the first time, organized the Open Day of Slovenian Clinical Laboratories, marking the 2nd October, the Slovenian Day of Clinical Chemistry and Laboratory Medicine. Laboratories throughout Slovenia opened their doors to the wider public and organized guided tours. Patients, journalists and other health professionals were invited to the laboratories, where they were shown our working environment and diagnostic procedures, and on that way bring the Laboratory Medicine close to the general population.

STANDARDIZATION AND HARMONIZATION IN LABORATORY MEDICINE IN CROATIA: CURRENT STATE AND FUTURE CHALLENGES

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Modern medicine is based on the values and quality of health care with health and safety of patients in the center. In the patient management system, laboratory medicine plays an important role because the results obtained in the laboratory are used in diagnosis, monitoring and treatment of diseases and provide the basis for clinical decision making. From a perspective of patients who are often diagnosed and treated in different medical institutions and / or health care systems, comparable, or harmonized test results across different measurement systems in different laboratories (time and location) become imperative. From clinician's perspective, only comparable results provide the basis for the use of same clinical guidelines, reference intervals, and interpretation of the results for a clinical decision. Besides, harmonization of the results of laboratory tests also increases the confidence in laboratory diagnostics and reduces the confusion of doctors and patients. An additional important aspect of harmonization is the benefit of sharing patients' results at various levels of the health system, often as part of patient's electronic records. Harmonization of measurements from different analytical systems is usually achieved by standardization and traceability of all procedures to the higher reference system. Although they are closely related and are often used interchangeably, harmonization and standardization relate to two different concepts of metrology principles. Standardization implies the traceability of results reported in SI (System International Units, SI) units to reference materials and / or higher order reference methods, while harmonization means consistency or comparability of measurement results. From perspective of laboratory and laboratory medicine, high standards of patient safety and medical care can only be met by controlling of the overall laboratory testing process (TTP), which includes the validation, implementation and monitoring of all pre- analytical, analytical and post-analytical processes in the laboratory. These procedures identify key quality indicators that are validated and improved over time. TTP quality assessment is carried out based on the guidelines and regulations adopted by national and international regulatory bodies.The quality of analytical processes is mostly based on IQC data and external quality assessment (EQA). In addition to checking and / or verifying the methods and measurement procedures used by the Medical Biochemistry Laboratories (MBL) and the regular performing of the IQC, the participation of the EQA program today is the »integrated professional activity of medical laboratories« and basis for improving activities that deliver high standards in quality medical care for patients. The term external quality assessment is used to describe a method or procedure that allows comparison of laboratory results with the results of other laboratories – comparative laboratories or reference laboratories. Although traditionally engaged in analytical quality, EQA is applied to other aspects of overall testing (pre-analytic and post-analytic processes) and has an educational, supportive and structured approach to improving laboratory results. Individual laboratory assessment and EQA play a central role in monitoring and promoting global initiatives towards standardization and harmonization of laboratory results. Based on this background, this presentation aims to present the results and challenges for the better interlaboratory comparability of MBL in Croatia, through the prism of two established tools: IQC and EQA.

MEDICAL BIOCHEMISTRY LABORATORIES AS PART HEALTH CARE SYSTEM IN SERBIA

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Serbia has inherited a health system financed by compulsory health insurance contributions, based on 10.3% payroll taxes (the Bismarck social insurance model). With the development of a private healthcare services and institutions for the last fifteen years, about 38% of expenditure for healthcare services in Serbia are paid out of pocket. The healthcare system was used to provide easy access to comprehensive health services for all

population. Health care in Serbia is provided through a wide network of public health care institutions owned and controlled by the Ministry of Health. Serbia has 261 state medical biochemistry laboratories, and 193 private laboratories registered at the Chamber of Biochemists of Serbia. In these laboratories work 295 Masters of Pharmacy-Medical Biochemists, 227 Medical Biochemistry Specialists (graduated at the Faculty of Pharmacy), and 276 Clinical Biochemistry Specialists, which are Doctors of Medicine. Education of specialist of medical biochemistry is equivalent with the EC4 register standards and they are responsible for complete laboratory organization and management from pre- to post-analytical phase, laboratory protocol preparation, internal and external quality control, laboratory accreditation etc. The licensing for medical biochemistry professionals was begin after the establishment of the Health Council in 2009 and license renewal depends on having collected a minimum number of points for accredited Continuous Medical Education activities. Educational programs have been accredited by the Health Council. According to the Guidelines on Conditions for Providing Healthcare medical biochemistry laboratories in Serbia are organized depending on the healthcare level – primary, secondary and tertiary. The Nomenclature of laboratory health services at the primary, secondary and tertiary level of health care have been applied since July 2012 (revision April 2018) and includes 1200 parameters of general laboratory and hematological analysis, analysis of hemostasis and biochemistry and immunochemical analysis. The quality of medical biochemistry laboratories services in Serbia is monitored at various levels with different indicators by supervisors and external laboratory auditing. Accreditation of biochemistry laboratories is not mandatory in Serbia. In the process of accreditation of healthcare institutions by the Agency for Accreditation of Health Institutions in Serbia (AZUS), an independent public agency, one of the requirements for accreditation is the assessment of the work of laboratory service. AZUS accredited 212 healthcare institutions. The Accreditation Body of Serbia (ATS) as the national accreditation body in Serbia offer an ISO 15189 and ISO 17025 accreditation for medical biochemistry laboratories. ATS has accredited 25 medical biochemistry laboratories, 11 as competent according to SRPS ISO 15189 and 5 according to SRPS ISO 17025. Very important role in continuous medical education has the Society of Medical Biochemists of Serbia that offers different programs and has significant publishing activity through Journal of Medical Biochemistry.

LABORATORY MEDICINE SPECIALIZATION TEACHING AND TRAINING IN BOSNIA AND HERZEGOVINA

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Heterogenity in definition of laboratory medicine and clinical chemistry that is present across Europe countries is also reflected on laboratory practice in Bosnia and Herzegovina. The situation regarding education and academic backgrounds of professionals in our country who are employed in medical laboratories is very complex. Further complications arise from the fact that Bosnia and Herzegovina is a Federation of two entities, each with their own laws and regulations. Ministries of Health from both entities regulate only the specialization field, and this law identifies MDs and pharmacists as candidates for medical biochemistry specialization that lasts for 48 months. Old specialization program that lasted 3 years included different programs for MDs and pharmacists. New 4 year program introduced in august 2015., is identical for MDs and pharmacists. Program includes theoretical lessons, medical biochemistry and laboratory medicine in duration of 18 months, hematology and coagulation 10 months, immunology 5 months, microbiology 2 months and clinical interpretations 8 months. During vocational training, occasional theoretical and mainly practical examinations are conducted. After the complete 4 year training, final exam is obligatory. The final exam is also theoretical and practical, and it is conducted by commitee composed of 3 distinguished experts in fields of medical chemistry and biochemistry. Currently in Bosnia and Herzegovina there are cca. 100 specialists in medical biochemistry field, of whom 20 are under age of 35 years. No complete official registration system exists. Almost all specialists are members of Association of medical biochemists in Bosnia and Herzegovina, which organizes yearly expert meetings as part of „life-long learning« process. For the purpose of assessing the quality of education in medical biochemistry, we conducted a survey among MDs and pharmacists currently in specialization program and young specialists by the questionnaire method. We concluded that education and specialization program in Bosnia and Hercegovina must be in accordance with The European Federation of Clinical Chemistry and Laboratory Medicine syllabus in order to ensure competent and expert specialists in the future.

LABORATORY MEDICINE IN HUNGARY

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Laboratory Medicine in Hungary is traditionally based on medical education. During the undergraduate studies students learn Clinical Biochemistry subject (lectures and seminars) in Hungarian/English/German languages during the 7th semester of the medical curriculum. After graduation the specialty training is for 5 years. The first 2 years (basic training) include laboratory skills and also healthcare practice in anesthesiology, internal medicine, emergency medicine, microbiology, pathology, etc. During the further 3 years the candidates acquire special skills from every major field of Clinical Chemistry. There is one year for conducting research activity. The whole training is financed by the government. After a successful specialty exam, the experts get full license for supervising routine laboratory testing. Beside medical doctors, there is a possibility for biologist, biochemists and chemists with MSc diploma to enter the 4-year specialty training named Clinical Biochemistry. For pharmacists we also have Clinical Laboratory Specialist training for 5 years. Specialty exams are complex, with practical and theoretical parts as well in all three types of postgraduate education. Regarding scientific activity, our Doctoral Schools accept medical doctors, biologists, chemists and pharmacists by an application procedure. Those who reach the highest degree can enroll to different doctoral schools. The PhD training consists of 2 + 2 years financed by the government in the form of scholarship. Certain foreign countries have an international contract with Hungary (Stipendium Hungaricum) to offer PhD training for foreign postgraduate students. The curricula and financing of this training is identical to those for Hungarians. Laboratory Medicine with all fields and full accreditation is done at the 4 Medical Schools in Hungary (Budapest, Debrecen, Pécs, Szeged). Besides these centralized laboratories we also have county hospital labs and smaller ones with only partial accreditation. Private laboratories also do routine testing but their number is limited at present. Most of the research activity (clinical and basic sciences) is done in the centralized big laboratories. The scientific impact of the Medical Schools seems to be the highest among the 4 universities in Hungary having Medical and Pharmaceutical Faculties.

LABORATORY SERVICE IN SMALL AND DIVERSE COUNTRIES – MONTENEGRIN EXPERIENCE

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Demanding world of laboratory diagnostic is constantly changing primarily due to the flood of technological innovations and progress of communication sciences. The constant need for diagnostic laboratories to improve quality and productivity, while reducing turn-around- time is causing laboratories to go through rapid consolidation process. But, in organization of laboratory service in our country, geographical and demographic features have played major rule. Majority of medical laboratories in Montenegro are public and funded by National health insurance and there are no private insurance schemes. All healthcare, including diagnostic, is delivered as primary, secondary and tertiary with well-defined panels of services. Samples in laboratories are processed or transported to nearest center with wither pallet, all laboratory managers supplied with guidelines for the collection and transport of specimens. Since interchangeable results are in the best interest of patients and potentially improve patient outcome, harmonization of laboratory testing is one of major goals of laboratory medicine scientists in our country. Aldo harmonization is focused on total testing process, from »pre-pre-analytical«, through analytical to the »post-post- analytical« phase, we have achieved major improvements in phases performed mainly by laboratories. Our future goals are to identify where harmonization is still lacking and involve relevant people (laboratory community, clinicians and laboratory specialist) and regulatory bodies to ensure optimal use and reporting of results, thereby minimizing misinterpretations. National quality control program is not organized and external quality control is not obligatory. Laboratories in our country, like elsewhere, are target for economic restrictions. For hospital inpatients laboratory testing is under diagnostic-related group (DRG), so reducing laboratory coasts will directly improve the profit of the hospitals. Process of regionalization of laboratory service has already started. As Society we will try our best to improve the role of laboratory diagnostics in patient management by upgrading every phase of testing process, so that real value of laboratory test – clinical information, not lack of available funds, becomes decision making criteria in selecting tests to be performed.

HARMONIZATION OF LABORATORY MEDICINE IN ALBANIA

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There is a vast European movement towards harmonization of the profession, aiming not only at the free movement of specialists but also at the harmonization of the patient service within all the European area. This harmonization is encouraged and guided especially by European and Global organizations as EFLM, IFCC and UEMS. Albanian Society of Laboratory Medicine and Laboratory Department, University of Medicine, Tirana, has constantly made efforts to harmonize of laboratory medicine in Albania. These efforts are conducted in: harmonization of post graduated education in laboratory medicine according European syllabus and directive; standardization of laboratory medicine by promoting and encouraging of accreditation ISO 15189; improvement of national standards and legislation in laboratory medicine field. Postgraduate training: Laboratory Medicine specialty in Albania comprises three branches: Clinical Biochemistry, Microbiology and Anatomic Pathology. Physicians graduated in 6 year program of medicine in public or private universities are candidate to follow the postgraduate program in laboratory medicine. The Laboratory Department, Faculty of Medicine, University of Medicine, Tirana, is the only one institution in Albania responsible for postgraduate training in laboratory medicine field. Based on the National Standards for Quality and Accreditation of Higher Education in Albania, in 2015 the Department of Laboratory reorganized and apply a 4 year clinical biochemistry postgraduate training syllabus which is firmly based on European recommendations of EC4 and UEMS recommendations. This improvement to the training syllabus seeks to achieve harmonization of profession according to EU requirements and recommendation. One of the objectives of the new syllabus is the medicalisation of the profession through the increase of the qualification of the specialists of the laboratory in areas where their role is essential, such as the interpretation of laboratory tests, giving advices and active participation in clinical consultations for solving complicated cases and so on. Focus on these areas directly affects the improvement of the service both for patients and clinicians. Accreditation ISO 15189: Accreditation of medical laboratories according to ISO 15189 standard is not obligatory in Albania. Since 2014 General Directorate of Accreditation, is the only national accreditation body in Albania, responsible for ISO 15189 accreditation. Only seven medical laboratories are accredited according to ISO 15189 in Albania; so the number of accredited laboratories is still very small. In recent years there is an initiative from Ministry of Health to reform and centralize the public hospital medical laboratories in Albania. It consists in the centralization and modernization of 18 public hospital laboratories through creating a network; Laboratory Department of University Hospital Center »Mother Teresa« will be in the center of this network. This reformation will renew all laboratory technology, standardize it, and implement a laboratory information system that will include the entire public hospital laboratory in the same network. All laboratories included in this network will be accredited according to ISO 15189 standard within the first 5 years. Harmonization, standardization and accreditation of medical laboratories are hot topics that need to take the necessary attention. Albania continues to make efforts to unify, standardize and harmonize laboratory medicine.

LABORATORY MEDICINE IN MACEDONIA: PAST, PRESENT, FUTURE

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Laboratory medicine was started almost 100 years ago in the First Military Hospital in Skopje. Malaria, tuberculosis, anemia, albumin, glucose, blood cells and urine sediment under microscope were detected in the laboratories. At the same time, analyses of urine (glucose, albumin, sediment) and blood (red blood cells and leukocytes) were made in the small laboratories that were part of private sanatoriums. Laboratories worked successfully until 1941. In 1950, the Central laboratory was founded in Skopje, and it performed activities related to biochemical diagnosis of patients hospitalized in the newly opened clinics (surgery, internal clinics, gynecology, dermatology, pediatric clinic, etc). Today, almost every clinic has its own laboratory. Each of them is equipped with the latest appliances for hematology, biochemical and immunological diagnosis. Specialization in medical biochemistry was introduced for the first time in 1960 and it lasted 3 years until 2008. The four-year specialization

program was designed at the Institute of Biochemistry, Medical Faculty in Skopje, according to the EU4 Directive and it is still in force. Doctors of medicine and masters of pharmacy can enrol to the specialization program. According to the health policy requirements, approximately 50% of the training process is dedicated to clinical chemistry (biochemistry), and the remaining 50% to transfusion medicine, haematology, microbiology, immunology, management. Within the scope of management, particular attention is put to leadership skills, organization of laboratories, communications with patients and colleagues, especially MDs from different medical branches.

LABORATORY STANDARDS IN BULGARIA. WHAT ELSE CAN BE IMPROVED?

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The primary goal of Laboratory Medicine is to provide information that is useful to assist medical decision-making and enables optimal health care. This type of information should be obtained irrespective of the measurement test kits and instruments, and of the laboratory where the procedure is carried out. It is therefore important to achieve a level of comparability of laboratory results among the many measurement procedures available so that results are harmonized and interchangeable over space and time. The standardization of measurements is therefore of high priority. In recent years, numerous efforts have been made at international level under the auspices of the IFCC and other organizations to standardize measurement results for many important analytes, e.g. enzymes, cardiac proteins, etc. The concept of standardization or establishment of metrological traceability has been developed to solve these challenges. Understanding the benefits of lab results traceability in public healthcare is of increasing importance, and enables the interpretation of results against common reference intervals, development of evidence-based clinical guidelines, and translation of research data into patient care and prevention activities, and the inclusion of lab data in electronic patient records. This presentation elaborates on the concept of standardization taking into account both the definite analyses (e.g., creatinine, cholesterol, glucose) and analytes, which have not been undoubtedly defined so far. In Bulgaria, there still exist huge differences in the analytical methods used as well as in the associated reference intervals, which could consequently significantly affect the proper assessment of patient health. In a constant effort to increase the quality of patients' care, there are numerous international initiatives for standardization and/or harmonization of laboratory diagnostics, which, unfortunately, are not so popular in Bulgarian laboratory practice, to enable maximum comparability of laboratory test results and improve patient safety.

DEMAND MANAGENT – FROM INNOCENT BYSTANDERS TOWARDS HANDS-ON APPROACH

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As long as professionalism of laboratory workers coupled with adequate funding enable continuous quality of service possible, communication between laboratory and external world is most commonly reduced to formal and faceless (either paper or electronic) interaction: referral on the one, and laboratory report on the other side. In such setting, issues involving quality of laboratory processes as well as prices of laboratory tests fall into a kind of black box, entirely unknown to users of our services, both patients and clinicians. The above-described situation of peaceful coexistence with minimum interactions might be altered in two possible scenarios: either because of restricted funding circumstances and emerging needs to economize or following the initiative to increase the value of our service through communication. In both cases the laboratory should spark those changes, taking into consideration primarily the possible savings and/or improvements in the quality of care. Therefore, laboratory professionals need to step out of laboratory enviroment and make themselves seen, heard and subsequently appreciated. We are not a faceless number factory, but it is us who must initiate that process. In this respect, the attitude that ordering laboratory tests is by no means laboratory responsibility represents nothing more than a passive submission to the path of least resistance. We should actually come out of the laboratory and, together with physicians, examine the potential space for rationalizing within the current laboratory test ordering protocols; more often than not, we should ourselves put forward concrete suggestions given that this problem area is far

closer to us than to clinicians. We should consult the literature and the ways in which numerous laboratories around the world have attempted to approach this issue. Each inadequate lab test that we have prevented makes room for the same or another test done in a patient who really needs this service. In our experience, the best way to prevent inadequate use of laboratory services is through introducing changes in the electronic interface used for requesting (introduction of minimal retesting intervals, reduced availability of certain tests on the request form, information about pricing). Such interventions may seem small, but each journey starts with the first step and proactive approach makes us visible, more equal and therefore more satisfied partners in the process of clinical care.

CAN LABORATORY PARTICIPATE IN HOSPITAL COST REDUCTION?

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Clinical laboratories are one of the most widely used parts of the health care system because they provide diagnostic services through a variety of tests. Laboratories play a key role in clinical decision and as a consequence 60% to 70% of diagnoses are based on the results of laboratory tests. In recent years, the demand for laboratory services has dramatically increased due to developments of new laboratory tests. This issue has led to an increase of laboratory costs. Today, laboratory services account for around 10% of total patient's costs. However, there is considerable variability in laboratory cost compared to total costs. Regarding to results of several studies, laboratory costs for more than 110 medical diseases are higher than 9,5% of total costs. According to the data of some hospitals in developing countries, the cost of consumable goods and laboratory tests was 22% and 49% of the total costs, respectively. In light of this evidence, laboratory professionals have a responsibility to control utilization of laboratory tests. There is a lot of opportunity for reduction of duplicate tests, errors and provision of better patients care. Overutilization and underutilization rate for laboratory tests is nearly a 30%. However, consequences of inappropriate testing leads to significant increase of cost, length of hospital stay, number of additional procedures and hospital visits. On the other hand, using targeted education and algorithm development, laboratory professionals can assist in reducing these costs. Modern diagnostic strategies are based on high classification level, high precision of diagnostic procedures including laboratory tests. All of this enables promptness of medical decision. Achievement of these goals could be possible through integration of new medical and biochemical data which altogether should enables decision making and consequently improvement of individual outcomes and cost-effectiveness of care.

ANALYTICAL QUALITY CONTROL BASED ON RISK MANAGEMENT

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Importance of laboratory test results in patient care management is well known. Inaccurate test results have many consequences which can result in staff effort, increased cost and time, and poor patient outcomes. Therefore, it is the responsibility of each laboratory to ensure accurate and reliable test results. The laboratory is a complex system thus many processes and procedures should be performed properly. Constant improvement is necessary in order to achieve the highest level of accuracy and reliability. Hence, the quality management system model is very useful for achieving good laboratory performance. Quality control was one of the first quality practices used in the laboratory and continues to play a vital role in assuring accuracy of testing. Quality control material should approximate the same matrix as patient specimens and should be treated in the exact same manner. Furthermore, the use of statistical models allows us to establish a significant change in the method performance and thus prevent the inaccurate test results. Today is well known that the internal quality control strategy cannot be the same for all methods performed in the laboratory. New laboratory guidelines recommend implementation of individual internal quality control strategy based on risk assessment for each method used. Implementation plan should identify the type and concentration level of control samples, specify the frequency of their determination, corrective actions and possible errors. Analytical method validation is the preliminary step in implementation of individual internal quality control strategy which indicates weather the test procedure is generally suitable for its intended use. Setting the acceptance criteria is a key point in order to reduce possible

errors and ensure the quality of test results. Internal quality control measurement frequency, the number of required control samples, and eligibility of results can be defined using the Six Sigma quality system. Sigma value is accepted as a universal measure of quality and can be used to assess the analytical performance of the laboratory processes. After defining the strategy, monitoring and analysis of performance, identification of unacceptable results and possible improvements, laboratory has to evaluate the rate of unacceptable results in order to quantify their incidence then use the Sigma quality system in order to assess the risk of unacceptable patient results. Only carefully designed internal quality control strategy can ensure the accurate and reliable test results.

FROM MEASUREMENT UNCERTAINTY TO EVERYDAY PRACTICE IN MEDICAL LABORATORY

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Many years passed after the first Strategic Conference that presented a consensus on the specifications that are necessary to achieve the proper quality of work in routine medical laboratories. But long before that, in the routine work of medical laboratories, the requirements of the good laboratory practice were met. The success of performing and fulfilling daily tasks in medical laboratories also depended on the control of the pre-analytical, analytical and post-analytical phases of the laboratory diagnostic, whose essence is to give the correct result that corresponds to the purpose of the clinical requirements of a physician. In order to harmonize the work process, in parallel with the application of the consensually proposed quality specifications, standards have been applied (ISO 17025 and 15189) related to the quality and competence of medical laboratories, and one of the required tasks is to analyze, calculate and present the uncertainty of the measurement of the results, as the ultimate representative product of the overall laboratory process. However, a pragmatic approach, besides understanding the concept of measured uncertainty in routine laboratory practice, should ensure a successful compliance with the requirements of the standards and should facilitate the implementation of the measurement uncertainty without affecting the costs, in order to ensure patient safety. For this, it is primarily necessary, on the basis of a common sense and conscience, to confirm and record various activities in routine work and to identify all possible shortcomings in everyday laboratory practice. In this way, it would be easy to contribute to the correct and regular laboratory organization and planning of the proper routine laboratory diagnostic. In addition, we must be aware of the importance of laboratory medicine in the entire health system and the necessity of continuous evaluation and continuous monitoring of the entire laboratory process, all in order to provide an effective contribution to the overall management of the patient. Although measurement uncertainty required by standards is a significant item that evaluates the measured result in medical laboratories, and which is successfully implemented in routine laboratory diagnostic, it is only one part of a much more significant diagnostic uncertainty that evaluates the whole testing process in everyday medical laboratory practice.

LABORATORY ROLE IN ACCREDITATION OF HEALTH CARE INSTITUTIONS IN SERBIA: AGENCY FOR ACCREDITATION OF HEALTH CARE INSTITUTIONS OF SERBIA – SURVEY POINT OF VIEW

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Accreditation of a healthcare institution is a procedure of assessment of the quality of work based on the application of an optimal level of established standards of work in healthcare institutions in certain fields of healthcare, or branches of medicine. Accreditation helps health care facilities to discover their own strengths and opportunities for improving the quality and safety of the patient and also to set short-term and long-term business objectives.. Accreditation process is designed to provide a framework that will enable health care facilities to

define and implement the necessary changes and make priorities for continuous improvement of their own services. Accreditation of a healthcare institutions in Serbia is conducted by Agency for Accreditation of Health Care Institutions of Serbia (AZUS). Accreditation is based on the standards that need to be met and it can be achieved by a series of activities that have been defined by criteria. Each standard has more than one criterion. In developing standards, the guidelines of the International Accreditation Program have been used. The standards are adapted to the principles for the development of accreditation standards for healthcare institutions defined by the International Society for Quality in Health Care (ISQua). Standards for the accreditation of a healthcare institutions include: Patient care standards, Support service standards, Standards of work of accompanying services, Leadership standards, Standards related to educational activities. For the accreditation of medical laboratory, there are 8 standards with 39 criteria. Members of the Society of Medical Biochemists of Serbia, as experts of working groups, had took part in defining laboratory standards and criteria on the basis of ISO standards, international and national recommendations and principles of good laboratory practice. Medical / clinical biochemists as surveyors appointed by the Agency for Accreditation of Health Care Institutions of Serbia, during visits to a healthcare institution, check compliance with the standards supporting this assessment with clearly documented evidence, identifying improvement opportunities and further development and making recommendations regarding deficiencies. Implementation of laboratory standards in the process of accreditation of healthcare institutions has contributed to the improvement of the laboratory work and the role of medical / clinical biochemists in a multidisciplinary team, improving communication with clinicians and better cooperation with other organizational units, which significantly improves the provision of health services in the diagnosis and treatment of patients.

LABORATORY ROLE IN ACCREDITATION OF HEALTH CARE INSTITUTIONS IN SERBIA: CHIEF OF ACCREDITED LABORATORY – POINT OF VIEW

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One of the main tasks for biochemists in modern medical laboratories is to obtain maximal benefit from all available technical solutions in order to optimize process of laboratory testing and to assure confidence in quality of laboratory results. Achieved level of competence should then be formally certified through accreditation process. Laboratory of Railway Health Care Institute was involved in process of accreditation as a part of accreditation of health care institutions in Serbia. During preparations which lasted about seven months, laboratory took a proactive role. We have supplemented all existing working instructions and procedures and systematized them according to requirements of Agency for accreditation of health care institutions of Serbia (AZUS). Also, we have introduced detailed evidence for each step of total testing process. Documentation of different criteria of accreditation standards was facilitated due to features of laboratory information system. Laboratory staff had positive attitude toward accreditation, especially in terms of standardization of operational procedures. First certificate of accreditation was assigned to our Institute for three years, and after additional improvements, at next evaluation we got AZUS certificate for seven years period. Thanks to implementation of accreditation standards, we've made better organization of total testing process, have precisely documented process management and made a step forward in assuring confidence in laboratory competence. All these issues contribute to improved laboratory quality and, more important, to improved patient safety.

IN VITRO DIAGNOSTICS AND EVOLVING REGULATORY CHALLENGES IN LABORATORY MEDICINE

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In vitro diagnostics (IVDs) provides objective information supporting »Evidence Based Medicine« constituting a basis for accurate and fast diagnosis which leads to appropriate and more effective therapy, targets drug treatments according to patient's response, causes reduction of morbidity, provides risk prediction and reduction, allows improved compliance, monitors recovery from disease and effects of treatment which allow for

reassessment and updating of therapy, shortens length of hospital stay, lowers risk of hospital infection, and improves the quality of life of patients. Clinicians are under increasing pressure for better clinical outcomes, and IVDs contribute positively to the quality of health care through screening, diagnosis, monitoring therapy, assessment of medical interventions and therapy. IVDs are a clear and rational investment in health care. IVDs have a broad scope ranging from sophisticated technologies at the cutting edge of research and development performed in clinical laboratories to simple self-test. The overall IVD market will double over the next 10 years, driven by an aging population and an increase in non-communicable and chronic diseases in both mature and emerging markets in spite of changes and challenges, increasing pressures to prove medical value, and a more stringent regulatory environment. The next-generation of POC platforms are expected to grow slightly faster than the central lab market. The in Vitro Medical Devices Directive (IVDD) 98/79/EC, introduced in 1998 was not capable of regulating all new technical and medical developments. Several weaknesses in the IVDD were identified: new developments regarding genetic testing and companion diagnostic devices that are not specifically addressed in the IVDD, the need to better align with international guidelines– including a risk-based classification system–and the lack of control over high risk »in-house« tests. The new European In Vitro Diagnostic Regulation (IVDR), published in the Official Journal of the European Union on May 5, 2017, entered into force on May 25, 2017. The official transition period to full implementation is five years. The biggest change is the introduction of a risk-based approach to classification in combination with increased Notified Body (NB) oversight. The new EU regulations create a new environment for IVD companies in terms of product development, management of product lifecycle, and commercialization approach. IVD companies need to re-register their entire IVD portfolio under the new regulation by the end of the five-year transition period. So, this will require additional efforts in terms of personnel and additional costs. The IVDR is applicable to all devices sold or marketed within the European Union (EU), with no distinction as to where they are marketed. CE Marking requirements, clinical and performance requirements, post-market vigilance and surveillance, a new device identification system based on Unique Device Identifiers (UDI) as well as a European databank on medical devices (EUDAMED) are introduced as new concepts for the IVDR. Clinical evidence demonstrates scientific validity, analytical performance, clinical performance, performance evaluation and their mutual relationship. IVD Manufacturers are required to develop post-market surveillance reports to monitor specific elements of safety, clinical performance, and risk/benefit ratios which may lead to a completely new infrastructure for innovation in the field of IVDs in the European Union.

LABORATORY MEDICINE IN ISRAEL: FOCUS ON NATIONAL HARMONIZATION OF CRITICAL VALUES COMMUNICATION

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Clinical Laboratories in Israel are functioning within various health care systems including in health maintenance organizations (HMO), in hospitals (Publics or belonging to HMOs) and in the private sector (one private hospital and a few private clinics). The private sector is minor in the Israeli healthcare system and most clinical laboratories are under the public system including regulation by the Israeli Ministry of health. In this context, the laboratory division in the ministry of health serves as a professional regulator of clinical laboratories operating in all the various healthcare systems. Regulation include a requirement for the clinical laboratories to operate under a quality assurance system (ISO 9001 or ISO 15186). In addition, all hospitals in Israel are required to comply under the Joint Commission International (JCI) accreditation system. The Israel Society for Clinical Laboratory Sciences (ISCLS), which is affiliated to the IFCC, is dedicated to the promotion and practice of clinical laboratory sciences. The ISCLS Vision is to lead in the provision of clinical laboratory services at the highest professional and academic level and to collaborate with our medical colleagues in striving for the best quality in patient care. In this context, we have initialized in 2018 a project whose goal was to present harmonization of the reporting process of critical values across all clinical laboratories in Israel in the field of biochemistry hematology and microbiology. This working process included seminars, surveys among labs directors and clinicians as well as presentation of the consensus values to all ISCLS members and publication in our website. In addition, a formal report of the consensus critical values including the associated guidelines for reporting critical values was presented to the national council for clinical laboratories in order to facilitate the issue of a formal regulation by the health ministry. The consensus values as well as the guidelines for critical values reporting will be presented in the lecture and academic publication is in preparation.

APPROPRIATE REQUEST AND INTERPRETATION OF LABORATORY TESTS: ASSESSEMENT OF MEDICAL RESIDENTS' SKILLS IN A ROMANIAN UNIVERSITARY CENTER

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Training in clinical laboratory is poorly represented in the general medical curriculum, resulting in junior doctors ordering unnecessary/inappropriate tests or requiring tests too frequently, as well as misinterpreting tests results. The aim of this study was to assess the level of self – confidence of medical residents from university hospitals in Cluj Napoca in ordering and interpreting some usual lab tests, and to identify their learning needs in that respect. The study had a cross-sectional design, and data collection was made through a questionnaire applied to residents from several specialties, from different training years. The questionnaire contained 29 usual biochemistry, hematology and coagulation tests, the residents being asked to ascertain how con dent they were in requesting the tests and interpreting the results. They were also asked about considering additional laboratory training and in which form they would prefer it (theoretical/practical/online training). The residents were also questioned about the action they would take when confronted with an unexpected test result (accepting the result without questioning, repeating request, contacting the laboratory staff for addressing the issue). Replies were received from 96 residents. The survey showed some areas in which residents are less confident about requesting tests and interpreting results (electrolytes, plasma proteins, red blood cells indices, coagulation tests). The study pointed out that the residents were overall more confident in requesting tests than in interpreting results. 78% of the respondents considered that they need specific training in that respect during residency. When confronted with what they considered a questionable result, 7% of the doctors took a decision based upon the result, 31.5% repeated the request and 57.5% discussed the results with the laboratory staff. The survey showed that the resident doctors in Cluj-Napoca have learning needs concerning appropriate test request and results interpretation, which could be addressed by specific additional training. Further development of the study would require the analysis of the differences (if any) according to specialty/year of training. Finding out more about those improvement needs, and properly addressing them could streamline the lab test requesting process on one hand, and benefit the patient on the other hand, which actually is the ultimate goal in medicine.

CHALLENGES AND PERSPECTIVES OF QMS-QUALITY MANAGEMENT SYSTEM: THE ROAD MAP FOR ACHIEVING STANDARDIZATION IN LABORATORY MEDICINE

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The constant work on improving QMS in health care system is one of the development mechanisms for upgrading and enhancing of health care. Standardization of conditions under the principles of good clinical practice (GCP), monitoring of modern medicine according to evidence based medicine (EBM) and good laboratory practice (GLP) reduces the possibility of action of various factors. Principles of good clinical practice are insured by application of total quality management system (TQM). The quality system is realized in accordance with the principles of focusing on users-doctors and patients, providing quality and timely services, informing and improving, following the progress of clinical-biochemical diagnostics, introducing modern and efficient testing methods, rational laboratory diagnostics, accurate and timely findings. The aim of this lecture is introducing the participants with clinical significance of accreditation and application of good clinical practice as well as activities on constant improving of health care quality in medical institutions. Participants will acquire professional knowledge and skills related to measures of improving the quality of health services, which refers to the improvement of all processes and services by eliminating unnecessary steps and activities through rationalization, applying Deming's PDCA concept to all activities related to quality. This means: P-plan, D-do, C-check, and A-act-constantly improve. Also the topic will cover health services that are needed to patients - do the right things, when a patient needs a service-work at the right time, using appropriate tests and procedures- work on the right way to achieve the best possible results and to improve the quality dimensions

of health care. Effectiveness of therapy according to clinical pathways and guidelines according to DRG (diseases related group), also interventions which will be applied to yield best positive results will be discussed. Safety – which means good clinical practice, good laboratory practice, good hygiene practice, practice of maintaining medical and related equipment, good practice of education and training, focus on patient and patient accessibility, equity and efficiency also will be mentioned. Measures for improving the quality of health services in medical institutions refer on the fundamental facility and factors of quality such as: personnel, education and training of employees, dependence on adequate equipment, innovation of services, quality and standardization of performed services through the application of quality management system.

LABORATORY DIAGNOSTICS OF ANTICOAGULATION

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For decades, a very limited number of anticoagulants were available in the clinical setting. Until recently, vitamin K-antagonists (VKA) were the only orally available anticoagulants, whereas parenterally mainly heparins were used. Through the years, many other »blood thinner« have been approved, culminating in the rise of the direct oral anticoagulants (DOAC), the direct oral thrombin inhibitor (DTI), Dabigatran, and four direct oral factor Xa inhibitors (DiXI), Rivaroxaban, Apixaban, Edoxaban, and Betrixaban. While monitoring of VKA and heparins is easily performed by prothrombin time (PT) and activated partial thromboplastin time (aPTT), respectively, testing for new anticoagulants is much more sophisticated. Only large central laboratories have an own specialized haemostasis department, capable of performing a broad range of coagulation testing. Some anticoagulants require routine monitoring of their effect, e.g. unfractionated heparins (UFH) and VKA, while others do not, e.g. all DOAC, Fondaparinux and low molecular weight heparins (LMWH). Testing of the latter is required only in special conditions, among them bleeding emergencies, perioperative settings and renal impairment. Measurement of UFH is done by aPTT-ratio, anti-factor Xa-activity (aFXa) or activated clotting time, while LMWH, the direct parenteral DiXI Fondaparinux and the orally available DiXI are monitored only by aFXa (calibrated against the respective anticoagulant). Parenteral (e.g. Argatroban) and oral (Dabigatran) DTI monitoring is preferably performed with diluted thrombin time calibrated against the substance in question, or with ecarin clotting time. DOAC are more and more prescribed and all clinical central laboratories nowadays must be able to perform DOAC screening (e.g. thrombin time, which is overly sensitive for DTI; aFXa for DiXI) for cases of emergency. Another topic is the fact, that certain coagulation tests, such as single coagulation factors and lupus anticoagulant, are non-determinable when different anticoagulants are present in the sample. However, there are several approaches to eliminate the specific anticoagulant in vitro, so that broad coagulation testing is feasible: heparinase enzymes cleave UFH and special charcoal formulations remove low molecular weight anticoagulants such as DOAC or Argatroban. As anticoagulant medications become progressively diverse and coagulation testing increasingly complex, a good collaboration and communication between the referring physician and the laboratory is of mounting importance. Data such as a) the used anticoagulant, b) the exact dosage, c) the last time of intake and d) other important clinical information are indispensable for the coagulation laboratory and should imperatively be provided by the assigning clinicians to ensure correct testing, interpretation of results and last but not least the patients outcome and safety.

ASSESMENT OF THE UTILITY OF DIFFERENT APTT REAGENTS IN TESTING LUPUS ANTICOAGULANT – REAL LAB SCENARIO

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Lupus anticoagulant (LAC) belongs to the group of antiphospholipid antibodies.The presense of LAC may be detected by clotting screen and depending on the reagents and method used, as well as on the potency and avidity of the antibody, either APTT may be prolonged. However, the sensitivity of APTT to LAC varies considerably, so that test may be normal. Using APTT with different LAC sensitivity in the laboratory, a different

result for LAC screen can be obtained. Although no single test is sufficiently sensitive to detect all LAC, recommendations for the optimal laboratory detection of LAC include: 1. two tests based on different principes; 2. DRVVT should be the first test considered; 3. The second test should be sensitive APTT; 4. LAC should be considered as positive if one of the two tests gives positive result. APTT reagents are composed of phospholipids with different source and concentration, and activators. aPTT reagents with low phospholipids and silica as activator are recommended for LA screening because of greater sensitivity. In this study we examined 1052 patients suspected for LAC, during 2009.–2015., with three different APTT reagents: Dade Actin FS (AFS), Pathromtin SL (PSL), Dade Actin FSL (AFSL), Siemens, in relation to the presence of LAC in plasma. The use of APTT/AFSL and dRVVT reagents together is the best diagnostic tool for assessing the presence of plasma lupus anticoagulant.

ASSESSMENT OF HYPERCOAGULABLE STATE IN NORMAL PREGNANCY AND PREECLAMPSIA USING GLOBAL HAEMOSTATIC ASSAYS

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Normal pregnancy is associated with significant changes in coagulation and fibrinolytic systems marked by enhanced thrombin generation, acquired resistance to activated protein C, increase in procoagulant factors and gradual decrease in anticoagulant factors and fibrinolysis. However this complex physiological adaptation to haemostatic challenge occurring during childbirth results in an increased susceptibility of pregnant women to thrombotic disorders. Haemostatic disturbances leading to hypercoagulability become more severe in preeclampsia (PE) indicating presence of procoagulant phenotype even after cessation of preeclamptic pregnancy. This serious pregnancy disorder of placental origin is characterized by vasoconstriction, metabolic changes, endothelial dysfunction, activation of the coagulation cascade, and increased inflammatory response. Furthermore, PE has high morbidity and mortality rates, and in recent years has been acknowledged as a risk factor for development of cardiovascular events (heart disease and stroke) later in life. Routine coagulation assays reflect acute situation providing static data on single coagulation factors, while traditional screening assays show limited sensitivity to hypercoagulant changes and inability to evaluate thrombotic risk. Nevertheless new generation of global haemostatic assays allow continuous monitoring of coagulation and/or fibrinolytic processes, and therefore enable evaluation of the balance between procoagulant and anticoagulant factors and give insight in all phases of haemostasis including initiation, propagation and inactivation. Widely used endogenous thrombin potential (ETP) assay measures the total amount and kinetics of thrombin generated over time, and thus reflects the thrombin-forming capacity of plasma beyond the initiation of clot formation. On the other hand, assay of Overall Haemostatic Potential (OHP) gives an additional insight into another important aspect of the haemostatic process, providing additional information concerning the rates of fibrin clot formation and degradation. Method is based on the determination of a fibrin aggregation curves with three derived parameters: Overall Coagulation Potential (OCP), Overall Haemostatic Potential (OHP) and Overall Fibrinolysis Potential (OFP), demonstrating the balance between the two opposed haemostatic entities.

HMG-CoA REDUCTASE INHIBITORS IN LIPID METABOLISM: DISCOVERY AND DEVELOPMENT

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Although commonly assumed to be a modern disease, signs of atherosclerosis were noted in 47 of 137 ancient mummies. 170 years ago Vogel demonstrated that cholesterol was present in arterial plaques, and in 1913 in St. Petersburg, Antischkow published that feeding of rabbits with cholesterol caused atherosclerosis. In 1960 Konrad Bloch and Feodor Lynen revealed the mechanism of synthesis and regulation of cholesterol (1964, Nobel Prize). After 50's in developed countries with boosting economy and increasing life spans and rather rich dietary habits, atherosclerosis becomes an increasingly important health problem. Epidemiologic investigations

established as major risk factor among others, the high blood cholesterol and intervention studies showed that lowering cholesterol levels would help reduce risk for CVD. Scientists began searching for drugs to lower blood cholesterol. Cholesterol-lowering agents like Nicotinic acid, Cholestyramine, Clofibrate and derivatives of it called fibrates, were developed but none of these could be considered ideal in terms of efficacy or safety. In the 1950s and 1960s, the research effort tried to find molecules that would block some steps in the biosynthesis of cholesterol. Akira Endo, a Japanese Biochemist, inspired by Fleming's success with molds, began his project using culture broths of thousands of fungi to find a potential inhibitor of HMG-CoA reductase, the rate-controlling enzyme in cholesterol synthesis. After many challenges he finally succeeded to discover Compactin, the first Statin in 1976. Brown and Goldstein who discovered the LDL receptor (Nobel Prize in 1985), confirmed the strong connection between HMG-CoA reductase activity and the functioning of the receptor. Soon thereafter it was shown that the HMG-CoA reductase inhibition increased messenger RNA for LDL receptors in the liver and the density of LDL receptors as well, on the surface of liver cells. Since then, 6 statins, including 2 semi-synthetic statins and 4 synthetic statins have been introduced to the market. Efficacy of statins as therapeutic drugs is related to their hydrophobic/hydrophilic properties. Some statins undergo extensive CYP450 metabolism, which can increase the likelihood of drug Pharmacokinetic interactions. Today statins are widely prescribed for treating atherosclerosis and about 30 million people worldwide are taking statins. They have shown benefit in reducing cardiovascular disease and mortality in those with few side effects.

THE CONTRIBUTION OF THERAPEUTIC DRUG MONITORING LABORATORY IN HEALTHCARE. CHALLENGES AND PERSPECTIVES

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Until the late 1960s and early 1970s, it has been customary practice for the physicians to adjust the dosage of drugs by trial-and-error processes. The clinical utility of TDM emerged when it became clear that not all patients have an optimum response to treatment. The surge of research work showed that the interindividual variability to the pharmacological response is due to factors named pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body). Therapeutic Drug Monitoring (TDM) is the measurement of specific drugs in body fluids, at timed intervals, usually at steady state and at distributional equilibrium, aiming at personalizing the dosage scheme, in order to maintain the drug concentration in the bloodstream in a target range namely therapeutic, that results in maximizing the efficacy and minimizing the toxicity of the drug. Various physiological, pathological and pharmacological factors contribute to the variability of the pharmacokinetic (PK) profile of a drug that determines the drug concentration in the bloodstream. The appropriate adjustment of the dose that results in maintaining the drug level into the therapeutic range minimizes the PK causes that affect the therapeutic response. Drug concentration monitoring is valuable mainly for long-term used drugs with narrow therapeutic index, high inter-individual variation in pharmacokinetics but low in pharmacodynamics, no good clinical markers of effect and appropriate analytical methods of measurement. A properly applied TDM is particularly useful in the following circumstances: assessment of compliance, individualization of treatment, control of drug-drug interactions, and investigation of overdose or suspected toxicity. For the implementation and benefit of effective and accurate TDM data, a number of requirements must be fulfilled such as: patient information, appropriate sampling time and specimen, valid analytical scheme, correct interpretation and response by the clinicians. The development of analytical methods with great sensitivity, specificity, precision and accuracy has expanded TDM services from the original measurement of digitalis to a broad spectrum of many important life-sustaining drugs such as antiepileptics, antibiotics, analgesics, immunosuppressive, antifungals, antiretroviral, antineoplastic, and psychoactive. Recently, a useful adjunct to the classical TDM (which is based on pharmacokinetics) has proved to be pharmacodynamics monitoring that focuses on the biologic effect of the drug on its target. Nowadays, a number of challenges are to be met, to ensure that TDM becomes a valuable tool in the treatment of many diseases e.g. measuring drug concentrations at the bedside in a timely manner, novel sampling strategies such as dried blood spot sampling, external quality assurance programs, improving assays for real-time pharmacodynamics monitoring by appropriate therapeutic biomarkers, algorithms to enable rapid and precise dosage adjustment, effective educational programs for the users of TDM services. Today, in the era of evidence-based medicine, the optimum dosage regimen-personalization strategy should meet at the convergence of classical TDM, pharmacodynamics biomarkers and of course pharmacogenomics.

THE INTEGRATION OF PHARMACOGENOMICS INTO CLINICAL PRACTICE

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Pharmacogenomics is a useful and revolutionary combination of pharmacology and genomics. In the post genome era, that is since 2002, after the publication of the human genome sequence, in order to display a more accurate description of patient's drug response, it is imperative to take into consideration not only the age, the gender, the lifestyle, the weight and the health status, but also to examine the genomic fingerprint. Pharmacogenomics offer the possibility to manage the inter-individual variability and personalize the medication s dose, that is to identify responders and non- responders, to avoid toxicity (adverse drug reactions, ADRs), to optimize the drug dose, according to Hippocratic injunction »Primum non nocere«, »μ« and in English »first, do no harm«. A patient's response, the pharmacokinetics and pharmacodynamics of a medication may vary with respect to the individual's alleles. The individualized treatment of a disease, the personalized choice and the individualized dosage of a patient offer an effective targeted treatment for a patient. The field of pharmacogenomic tests is rapidly expanding. More than 200 drugs already have pharmacogenomics biomarkers' information on their labels and package inserts (https://www.fda.gov/drugs/scienceresearch/ucm572698.htm). Pharmacogenomics tests make sure and focus on the well-known 5 rights of medication administration: that the right patient receives the right drug at the right time, in the right dose, by the right route. The majority of pharmacogenomics biomarkers' information concern anticancer therapy. The Pharmacogenomics Knowledge Base (www.pharmgkb.org) is a source of information on the genetic variation of drugs response. It includes clinical information: drug labeling, potentially clinical gene–drug interactions, genotype–phenotype relationship and dosing guidelines. Given the whole-genome sequencing rate cost shrinkage in the last years, pharmacogenomics tests can be readily applicable to the clinical practice.

PHARMACOGENOMIC APPROACH IN DEFINING SENSITIVITY TO SSRI THERAPY, EXPLORING REGULATION OF GENES CODING ITGB3 AND CHL1

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Pharmacotherapy of major depressive disorder (MDD) is facing many challenges for decades. Selective serotonin reuptake inhibitors (SSRIs) are the first-choice drugs in modern antidepressant and anxiolytic pharmacotherapy; however, only about a half of the treated patients reach the remission state. Thus, personalized therapy based on the pharmacogenomic findings would be of great advantage in the future. Our previous in vitro genome-wide transcriptomic study on human lymphoblastoid cell lines exposed to the SSRI paroxetine for 21 days indicated that this treatment resulted in nearly two-fold increase of integrin 3 (ITGB3) gene expression, while it was demonstrated that ITGB3 protein up-regulates the serotonin reuptake transporter (SERT) activity. Also it was found that ITGB3 expression in PBMC was reduced in non-medicated MDD patients compared with healthy controls. Close homolog of L1 protein (CHL1), another brain-expressed cell adhesion protein, was also implicated in the mode of action of SSRIs, and based on in vitro studies, it was proposed that relative ratio of ITGB3/CHL1 and SERT could be linked to sensitivity to SSRI therapy. In a model of stress-induced depression we investigated expression of ITGB3, CHL1, ITGAV and SIRT1 in prefrontal cortex, and weather its' changes are associated with antidepressive effect of the SSRI citalopram and neuropeptide oxytocin in vivo. The study showed that in prefrontal cortex ITGB3 expression was reduced in a MDD model, while oxytocin and citalopram treatment attenuated this reduction. In addition, pro-anxiolytic parameters were positively correlated with PFC ITGB3 expression, while pro-depressive parameters were correlated with the PFC CHL1 expression. Thus, findings obtained in vivo complemented previous in vitro findings and further support the hypothesis of the role of ITGB3/CHL1 in sensitivity to SSRIs. Also, present findings imply that defining level of expression of these two genes in MDD patients could potentially help clinicians to predict outcome of the pharmacotherapy with SSRIs, and advocate for the broader relevance of the pharmacogenomics research.

ENDOCRINE DISRUPTING CHEMICALS INDUCE OXIDATIVE STRESS

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Endocrine disrupting chemicals (EDCs) are naturally occurring compounds, but generally they are synthetic, found in thousands of products such as plastics, industrial chemicals, fuels, pesticides, fungicides, cosmetics and pharmaceuticals. They are used as preservatives in food and cosmetics, as plasticizer in toys and medical devices. EDCs can modify signals by inhibiting or activating them, that result in the malfunctions in the endocrine, developmental and reproductive system. Also, EDCs induces neural, immune health problems such as infertility, polycystic ovarian syndrome, endometriosis, reproductive tract anomalies, metabolic syndrome, obesity, hypertension, insulin resistance, diabetes, and dyslipidemia and multiple types of cancers. EDCs either natural or man-made, alters the receptor and enzyme activities that change the cellular metabolism and cellular communications to respond to the kind, concentration and exposure time. We have analyzed the regulatory enzyme activities that control the oxidized and reduced form of glutathione that affect oxidative stress. The metabolic end product of EDCs may be more toxic then the substance itself. Therefore, we analyzed the effects of these EDCs in detoxification pathways that depends on the successful completion of five enzymatic reactions; G6PD (Glucose-6-phosphate dehydrogenase), 6- PGD (6-phosphogluconate dehydrogenase), GST (Glutathione S-transferase), GPx (Glutathione Peroxidase) and GR (Glutathione reductase) activities were measured. Our data showed that, these enzyme activities were significantly affected due to type, concentration and exposure time.

WHAT ARE ENDOCRINE DISRUPTOR CHEMICALS AND THEIR EFFECTS ON THE ORGANISMS?

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An endocrine-disrupting compound was defined by the U.S. Environmental Protection Agency (EPA) as »an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process.« Endocrine- disrupting chemicals (EDCs) were originally thought to exert actions primarily through nuclear hormone receptors, including estrogen receptors (ERs), androgen receptors (ARs), progesterone receptors, thyroid receptors (TRs), and retinoid receptors, among others (Kandarakis et al., 2009). The group of molecules identified as endocrine disruptors is highly heterogeneous and includes synthetic chemicals used as industrial solvents/lubricants and their byproducts [polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins], plastics [bisphenol A (BPA)], plasticizers (phthalates), pesticides [methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)], fungicides (vinclozolin), parabens and pharmaceutical agents [diethylstilbestrol (DES)]. Natural chemicals found in human and animal food (e.g., phytoestrogens, including genistein and coumestrol) can also act as endocrine disruptors. These chemicals are a group of endocrine-disrupting chemicals that accumulate at high concentrations in air, soil and aquatic environment with the use of detergents, paints, pesticides and plastic manufacturing. They are also found in the fluids and body fat of animals and humans (Céspedes et al., 2008; Kumaran et al., 2011). Due to their lipophilic properties, these compounds may accumulate in the body fat. BPA and phthalates are used in the manufacture of epoxy, polycarbonate and corrosion-resistant unsaturated polyester-styrene resins required for food packaging materials in industrial processing (Knaak and Sullivan, 1966; U.S Department of Health and Human Services, 1982; EFSA reports, 2017). The US Food and Drug Administration (FDA) have taken steps to reduce BPA exposure with food supplies and the US Environmental Protection Agency (EPA) has added BPA to the list of target chemicals (U.S. Environmental Protection Agency, 2010). The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong and there is mounting evidence for effects for effects on other endocrine systems, including thyroid, neuroendocrine obesity and metabolism, and insulin and glucose homeostasis.

IMPACT OF THE DI-2-ETHYLHEXYL PHTHALATE-INDUCED OXIDATIVE STRESS ON THE TISSUE DAMAGE

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Di(2-ethylhexyl) phthalate (DEHP) belongs to family of the endocrine disrupting chemicals (EDCs) and widely-used as synthetic polymer in the industrial products including toys, medical devices, cosmetic products and food packagings. There is a growing concern about adverse health effects of DEHP, since it can impair the reproductive and developmental system in human and wildlife. Also, DEHP can induce carcinogenesis, diabetes and obesity, however DEHP-induced oxidative stress and its relation to the tissue damage has not been widely studied before. Our aim was to investigate influence of the DEHP on the oxidative stress metabolism in relation to the tissue damage in rats. 24 prepubertal male rats were randomly divided into the four groups and dosed with 0, 100, 200, 400 mg/kg/day of DEHP. Trace element and mineral levels, glucose-6-phosphate dehydrogenase (G6PD), 6-phosphogluconate dehydrogenase (6-PGD), glutathione reductase (GR) and glutathione S-transferase (GST) enzyme activities were evaluated in serum, liver, and kidney samples of rats. Serum clinical biochemistry parameters, organ/body weight ratios and histopathological changes were evaluated as well. Our data showed that anti-oxidant enzyme acitivites significantly changed upon tissue damage in the kidney and liver samples. Also we observed significant histopathological changes indicating tissue damage in the DEHP-administered rat tissues. Moreover, DEHP caused imbalance in the biochemical parameters and trace element levels in serum, kidney and liver samples of rats upon DEHP administration. In conclusion, DEHP is able to induce oxidative stress and cause imbalance in the biochemical parameters that result in the kidney and liver damage in rats.

THE INFLUENCE OF DI-2-ETHYLHEXYL PHTHALATE ON THE FATTY ACIDS COMPOSITION

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DEHP is commonly used phthalate in the polyvinylchloride (PVC) formulas including medical devices, toys and food packaging. DEHP belongs to the endocrine disrupting chemicals (EDCs) family that impairs endocrine, reproductive and developmental system. DEHP can induce lipid metabolism resulting in the heart diseases, diabetes and obesity. We aimed to investigate influence of the DEHP on the liver, kidney and spleen tissues since these tissues are responsible for the detoxification of DEHP. 24 prepubertal rats were randomly divided into the four groups and dosed with 0, 100, 200 and 400 mg/kg/day. Tissues were homogenized in methanol and in situ direct transesterification method was used to provide fatty acid methyl esters (FAMEs) for determination of fatty acid profile of the rat tissues. FAME extract from each sample was analyzed by a 7890-B Agilent GC equipped with a 5977A Agilent MSD detector and DB-23 column. Our data showed that FAME content significantly changed in DEHP treatment groups compared to the. In conclusion, DEHP is able to disrupt lipid metabolism and cause abnormalities in the FAME composition.