SPEAKERS' SUMMARIES

Wednesday, October 10th 2018

Hall A

18:00-19:00

Opening Lecture

Laboratory Medicine – Challenges And Opportunities

Michael Oellerich[1]
[1]University Medical Center Göttingen, Dept. of Clinical Pharmacology

The changes occurring in laboratory medicine imply that there is a risk of it becoming more a service and less an academically oriented profession. The main forces currently driving clinical laboratory organization involve outcomes-based healthcare with the goals of improving quality and patient safety, containing costs and delivering more value for money. Further factors are technological advances, including laboratory automation, digitalization, molecular diagnostics, and new Point-of-Care solutions. Economic pressures result in increasingly limited budgets with consolidation and regionalization of laboratory services. Consequences of healthcare cost reductions include fewer positions for academic clinical laboratory directors, downsizing of post-doctoral training programs, and less time for research because of increased clinical service demands. These developments pose major structural risks, as laboratory medicine may be viewed by health policy makers primarily as a service unit. The development of value-based strategies is important to reverse these trends. Value in healthcare is described as "outcomes relative to costs". Advanced diagnostics (molecular and genetic tests) will contribute to a move from a volume- to a value-based system. As an example, genotype-directed cancer care is gaining increasing importance, as noninvasive genotyping of circulating cell-free tumor DNA in plasma can be used for personalizing therapy. In transplantation, graft-derived cell-free DNA can be used to detect rejection episodes at an early, actionable stage and help to personalize immunosuppression. The concept of Value Proposition for laboratory medicine allows for the assessment of the contribution of laboratory tests to economic efficiency in healthcare. Value Proposition for laboratory medicine is expressed in terms of outcomes; from guiding clinical decision making, process of the care delivered, and resources required to deliver that care. The role of laboratory medicine should be enhanced through participation as an integral member of the healthcare team instead of being only a service provider. Laboratory medicine should implement scientific innovations into diagnostics, develop value-based strategies for advanced diagnostics, take leadership in how tests are used, and generate the Value Proposition. Laboratory medicine should be a driver that ensures multi-disciplinary cooperation to best promote personalized medicine. This would benefit patients and the healthcare system by shifting the emphasis in medicine from reaction to prevention, facilitating targeted therapy, reducing trial-and-error prescribing, reducing adverse reactions, and increasing the cost-effectiveness of healthcare.

Regarding the future of laboratory medicine, we can be optimistic that, despite all challenges, the current pace of innovation will provide an environment in which our discipline has a chance to grow as an academic profession. EFLM-UEMS joint congresses are an important platform for communication of innovations and value-based strategies, as well as for increasing the visibility of laboratory medicine.

Keywords : Laboratory medicine, value proposition, personalized medicine, value-based healthcare

Thursday, October 11th 2018

Hall A

09:00 - 10:30

S4.Diagnostic approach to hemostasis disorders

Coagulation testing and new oral anticoagulants (Sophie Testa)

Thrombin generation analysis: research tool, biomarker or intermediate phenotype?

Tilman M. Hackeng[1]
Maastricht University

To accurately assess presence of functional coagulation disorders, global coagulation tests reflecting in vivo blood coagulation are used that apply natural initiation, progression, and termination routes. While thromboelastography enables establishment of haemostasis in full blood and is ideally used in the clinic to monitor and treat bleeding of individual patients, calibrated automated thrombin generation (CAT) or thrombin generation analysis (TGA) in practice uses citrated plasma and is therefore more suited to investigate large populations or cohorts of patients.

Diagnostic Approach To Hemostasis Disorders

Hugo Ten Cate[1]
[1]CARIM and MUMC

Traditionally, disorders in hemostasis (bleeding, or thrombosis) were diagnosed based on clotting assays; any major defect in one of the coagulation pathways, would be revealed by a prolongation of a clotting time, upon stimulation of plasma with an appropriate agonist. This way, diseases like hemophilias (deficiency in factor VII, IX or XI) could be detected, at least when the respective clotting factor was present at markedly reduced quantities.
The opposite, a thrombosis tendency, was hard to detect with conventional clotting assays. This was one reason for developing more sensitive, integral assays for detecting defects in, or excess activity of, the coagulation system. Ideally, all relevant components of blood coagulation would be present in such an assay (vessel wall cells, whole blood). To approach this, combinations of different components were used to develop integral tests, that reflect at least substantial parts of the coagulation system; these include thrombin generation analysis (TGA), or assays that have fibrin formation (and lysis) as endpoint, thromboelastography (TEG) and rotational thromboelastometry (ROTEM).

For TGA one can distinguish different applications: 1. detect (risk of) thrombosis; 2. detect risk of bleeding; 3. monitor and adjust therapy (pro-hemostatic, or anticoagulant); 4. address mechanisms of disease.

Detecting a risk of venous thrombosis is particularly relevant in patients that have been treated with anticoagulants and in whom cessation of this therapy is considered. The magnitude of increase in TG after stopping anticoagulants is associated with an increased risk of recurrent thrombosis. In patients with arterial thrombosis risk, the direction of risk associations of TG and thrombosis is less predictable; both positive and negative associations have been seen and most likely, the use of platelet rich plasma (PRP) is required in order to better reflect the clinical condition of arterial thrombosis (in which platelets are dominant players). Recent data show that TG done in PRP shows correlations with inflammatory mediators, that support the thrombo-inflammatory nature of arterial thrombosis.

Detecting a risk of bleeding is important in the optimal management of patients with haemophilia, but also in the peri-operative setting (reduced TG associated with increased risk of bleeding), as well as in the management of thrombotic disorders with various anticoagulants. While surgical settings probably require TEG/ROTEM technology for optimal transfusion management, rather than TG, the latter may find

a place in guiding specific therapeutic interventions in haemophilia, which I will briefly address. TGA may be of interest to detect anticoagulant effects, induced by (lower doses of) direct oral anticoagulants or vitamin K antagonists, however

the possible relationship with bleeding risk remains to be determined. Finally, TGA has been shown to be of value in detecting underlying mechanisms of thrombosis and bleeding, both in patients and in experimental conditions (animal experiments, or in vitro studies.

One can conclude that TGA, like other integral coagulation assays, offers unique possibilities to address mechanisms of bleeding and thrombosis, while the applications in routine care are still at the horizon. Distinct use in the management of patients with complex bleeding disorders, or with individually tailored oral anticoagulants, may at the short term be feasible applications of TGA in clinical practice.

Keywords : Keywords : thrombin generation, thrombosis, anticoagulant, haemophilia

Thursday, October 11th 2018

HALL A

10:45 - 11:30

Plenary Lecture : Liquid Biopsy For Cancer Screening

Plasma diagnostics of cell-free nucleic acids in malignant disease: towards actionable health information in Laboratory Medicine

Michael Neumaier, MD PhD

EFLM President

Institute for Clinical Chemistry, Medical Faculty Mannheim of Heidelberg University, Mannheim, Germany

The detection of malignant disease has been among the most daunting challenges for Laboratory Medicine for a number of reasons. To acknowledge the importance of the recent analytical developments, one needs to appreciate the methodological capabilities available in routine diagnostic health care so far.

Traditionally confined to the phenotypic analysis in blood and bodily fluids, laboratory diagnostics had to rely on surrogate markers as defined by monoclonal antibodies since the 1980s. The vast majority of these markers are normal tissue differentiation antigens - mostly proteins - and are by no means “tumour-specific”, but rather “tumour-associated” and thus are not recommended for early and primary diagnosis. Importantly, no markers exist in Laboratory Medicine to assess tumour variability, dignity and tissue of origin, internal microheterogeneities and dynamic biological properties, the tumour´s different metastatic capacity or ability to lie dormant for years.

Irrespective of the limitations of phenotypic analysis, all tumours feature molecular defects for the initiation of malignant growth and progression of systemic disease. With the advent of Genomics and functional Genomics, these defects are routinely being investigated by the Molecular Pathologist as specific genomic footprints in the tumour tissue.

Recent advances in molecular methods now allow the identification of these tumour-specific genetic footprints in blood and bodily fluids, thus changing the tables for Laboratory Medicine. As genetic defects constitute potential targets for new biomolecular therapies e.g. antibodies or small molecules, the molecular tumour profiles of circulating tumour-derived cell-free nucleic acids in blood (liquid profiling) represent actionable health information with direct impact for clinical decision-making. There is a rapidly

increasing body of literature demonstrating the implications of liquid profiling (aka liquid biopsy) for therapeutic decisions, early detection of therapy failure due to escaping mechanisms. Very recently, the combination of proteomic approaches in combination with the detection of circulating tumour-DNA has been suggested for early primary diagnosis and possibly for screening for some cancers (1). Interestingly, the "protein diagnostic arm" in this study really represented well-known classical serum tumour markers like CEA, PSA, CA-125 and others.

The presentation will focus on the systematic principles, recent analytical advances and their implications and the potential that a combined genotype/phenotype strategy may have for future improved cancer diagnostics in Laboratory Medicine.

Literature

1) Cohen JD et al. Science (2018); 359 (6378), 926-930

Thursday, October 11th 2018

Hall A

13:00 - 14:30

WASPaLM Symposium

Perspectives On Women's Health Care: Novel Approaches For Rare Diseases, Aging And Cancer

Cinzia Marchese[1],Francesca Megiorni [1],Enrica Vescarelli[1],Simona Ceccarelli[1]

[1]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

The identification of new therapeutic targets or biomarkers is a specific hallmark of Clinical Pathology and Laboratory Medicine, but the recent advancements in biotechnology pointed out that services offered by the laboratory to the medical community should also include the development and production of cell-based and tissue-engineering applications for pathologies with limited treatment options and for rare diseases.

Our group is particularly involved in issues related to women's health care. In this field, we developed a revolutionary approach to treat patients affected by Mayer-von-Rokitansky-Kuster-Hauser (MRKH) syndrome, a rare disease that occurs in 1/4500 females and is characterized by vaginal agenesis. The surgical reconstruction of a neovagina is the most common treatment option for these women. Between 2006 and 2016, our laboratory and clinical team has followed and treated a consecutive series of 39 women with MRKH, performing vaginoplasty with a modified Abbè-Mclndoe technique using autologous in vitro cultured vaginal tissue, obtained from a full-thickness mucosal biopsy of the vaginal vestibule. This tissue-engineered-medicine-based approach is characterized by the fast availability of the biological product (20-30 days), the minimally invasive procedure (with no abdominal approach) and the final result ensuring an anatomically and functionally normal vagina, since it is elastic and lubricated thanks to the presence of interspersed cells important for the spontaneous mucus production.

Another topic of special interest for our laboratory in the context of women's health care is represented by menopause. It is characterized by estrogen deficiency, which in turn might cause systemic symptoms, including night sweats, hot flushes, mood fluctuations and cognitive changes. Estrogen loss also induce vaginal symptoms (dysuria, pain, mucosal atrophy and vaginal drying) that represent a significant health concern for the female population as they can occur also in premenopausal women following local treatments for endometrial cancer, such as vaginal brachytherapy. Treatments based on local estrogen administration have been seriously questioned, as topic estrogens can reach the bloodstream, thus leading to consider their safety as controversial especially for patients with a history of breast or endometrial cancers. In our laboratory, the availability of in vitro mucosal cell cultures obtained from biopsies of the vaginal vestibule has represented a useful tool to evaluate the efficacy of new therapeutic strategies for vaginal atrophy. Recently, growth factors have been shown to

interact with the estrogen pathway, so we investigated the proliferative effect of keratinocyte growth factor (KGF), a known mitogen for epithelial cells, on human vaginal mucosa cells, and its in vivo efficacy on vaginal atrophy in a murine model. We demonstrated that KGF restores vaginal trophism similarly to intravaginal estrogenic preparations, without systemic effects, thus suggesting its use as an alternative therapy for vaginal atrophy. An international patent has been registered for this product. In conclusion, the increasing involvement of the laboratory in translating scientific discoveries into patient care, often referred to as a "bench to bedside" process, should lead the Laboratory Medicine community to encourage specific protocols for the development of advanced therapies and their faster application into clinical practice.

Keywords : Regenerative Medicine, Women's Health, Menopause, Rare diseases, Cancer

Inositol Metabolites As Biomarkers Of Peripheral Complications İn İnsulin Resistant And Diabetes Patients

Mariano Bizzarri[1],**Roberto Verna**[1]
[1]Department of Experimental Medicine, Sapienza University, Rome, Italy

Alterations of intracellular levels of myo-inositol (MI) as well as deregulated inositol metabolism can significantly influence a number of cellular processes as signaling pathways and osmotic balance. Reduced availability of inositol-phosphoglycans (IPGs) have been shown to hinder insulin signaling, while appropriate intracellular MI content efficiently counteracts the activation of the aldose-pathways. Moreover, depletion of MI and IPGs have been implicated in the etiology of renal and peripheral neurologic complications of diabetes. Inositol and its intermediate metabolites levels resulted significantly altered in diabetic patients: urinary excretion of IPGs is usually higher in diabetic patients and correlates with glucose plasma values. Inositol is catabolized in the kidney by the myo-Inositol oxygenase (MIOX), thus leading to increased release of toxic oxidized inositol metabolites, like D-glucaric acid (GA). Detectable levels of MIOX have also been recorded in extra-renal tissues like the retinal pigmented epithelium and some peripheral nerves. These results indicate that MIOX activation may lead to increased production of oxidative toxic metabolites in those tissues where diabetic complications, including nephropathy, neuropathy, retinopathy, and cataract, are frequently observed. Our data suggest that analytical determination of MI and its main metabolites (IPGs and GA) can significantly help in diabetes diagnosis and staging and eventually in monitoring clinical response to anti-diabetic treatment.

Keywords : diabetes; inositol; inositol-phosphoglycan; MIOX; diabetes nephropathy; diabetes markers

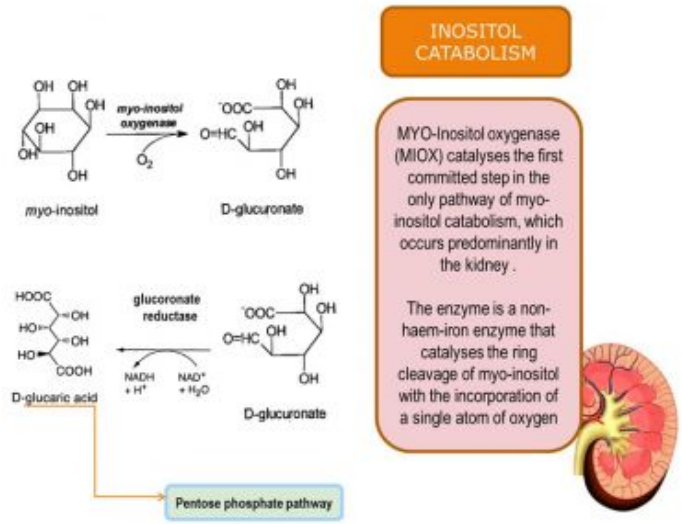

Figure Title: Myo-Inositol catabolism

Usefulness of intraoperative parathyroid hormone monitoring during minimally invasive video-assisted parathyroidectomy (Elisabetta Stenner)

Thursday, October 11th 2018

Hall A

14:45 - 15:45

S16. Pediatric Laboratory Medicine

Newborn Screening For Metabolic And Lysosomal Diseases

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Background: Newborn screening is program that has to be evaluated continuously. Increased propionylcarnitine levels in newborn screening are indicative for a group of potentially severe disorders including propionic acidemia (PA), methylmalonic acidemias and combined remethylation disorders (MMACBL). This alteration is relatively non specific, resulting in the necessity of confirmation and differential diagnosis in subsequent tests. Thus, we aimed to develop a multiplex approach for concurrent determination of 3 hydroxypropionic acid, methylmalonic acid and methylcitric acid from the same dried blood spot (DBS) as in primary screening (second tier test). We also set out to validate the method using newborn and follow up samples of patients with confirmed PA or MMACBL.

Patients/Methods/Results: The assay was developed using liquid chromatography–tandem mass spectrometry (LC-MSMS) and clinically validated with retrospective analysis of DBS samples from PA or MMACBL patients. Reliable determination of all three analytes in DBS was achieved following simple and fast (<20 min) sample preparation without laborious derivatization or any additional pipetting steps. The method clearly distinguished the pathological and normal samples and differentiated between PA and MMACBL in all stored newborn specimens. Methylcitric acid was elevated in all PA samples; 3 hydroxypropionic acid was also high in most cases. Methylmalonic acid was increased in all MMACBL specimens; mostly together with methylcitric acid.

Conclusions: A LC-MSMS assay allowing simultaneous determination of the biomarkers 3 hydroxypropionic acid, methylmalonic acid and methylcitric acid in DBSs has been developed. The assay can use the same specimen as in primary screening (second tier test) which may reduce the need for repeated blood sampling. The presented findings suggest that this method can reliably differentiate patients with PA and MMACBL in dried blood. We expect that a considerable number of children will benefit from screening for additional target disorders, in the course of the pilot study „Newborn screening 2020”and in the case of a future comprehensive extension of the newborn screening panel for Germany.

Keywords : Metabolic disorders, Newborn screening, Second-tier

The role of laboratory in diagnosis and management of familial hypercholesterolemia

Luis Masana[1]
[1]**“Sant Joan” University Hospital**

One out of two hundred and fifty children have Heterozygous Familial Hypercholesterolemia (HeFH), however the disease is under detected particularly in children. The mean diagnosis age is approximately 40 y/o precluding any early intervention as lifestyle advice or drug therapy if necessary. HeFH is clinically silent and clinical scores like the Dutch Lipid Clinics Network cannot be used in children; therefore, detection strategies are warranted. Several protocols have been implemented as universal

genetic screening or screenings based on total cholesterol measurements. While universal genetic screening will detect any affected individual, the low positive rate (4/1000) makes difficult to implement it. A strategy based on a child to parent pathway, where parents of children with high cholesterol are examined first, including genetic testing if necessary, leads to a reasonable clinical yield. In our hands this approach, implemented in collaboration with primary care paediatricians covering a 63500 children population of, allowed us to detect 38 affected children (75% genetically positive) from 110 suspicious index cases from. By detecting the affected parents the genetic test in children can be directed to the known mutation saving time and money.
An important point is how to distinguish FH from non-FH hypercholesterolemic children. In this area we have explored different biochemical markers. Lipid profile examined by new generation 2D-1H-NMR (www.biosferteslab.org) gives a more precise view of circulating lipoprotein particles and their defects. HeFH have more small LDL particles, but just because they have more LDL. The relative proportion is not changed although modifications in other particles can be observed.

We have also explored other biomarkers as circulating proteins associated with the LDL receptor. Both IDOL and PCSK9 is increased in FH children although only the first one seems to improve the discrimination between FH and non-FH hypercholesterolemic children. Interesting, circulating soluble LDL receptor levels are paradoxically increased in FH children suggesting that a functional defect doesn't implies a low protein production.

Physicians have the commitment of improving FH diagnosis in children and only an appropriated strategy combined with informative new biomarkers will drive to a better genetic result.

Girona J et al. Plasma IDOL,Soluble LDLR and PCSK9 Levels as Potential Biomarkers of Familial Hypercholesterolemia in Children. J Clin Lip 2018.

Rodriguez-Borjabad C et al. Lipoprotein profile assessed by 2D-1H-NMR and subclinical atherosclerosis in children with familial hypercholesterolaemia. Atherosclerosis, 2018.

Ibarretxe D et al. Improving The Detection Of Familial Hypercholesterolemia By Actively Searching For Affected Children: The Decopin Project. Under review.

Thursday, October 11th 2018

Hall A

15:45-16:15

S3. The Utility Of Biomarkers In Neurological Disorders

The Diagnosis And Managemet Of Demantia

Sylvain Lehmann[1]
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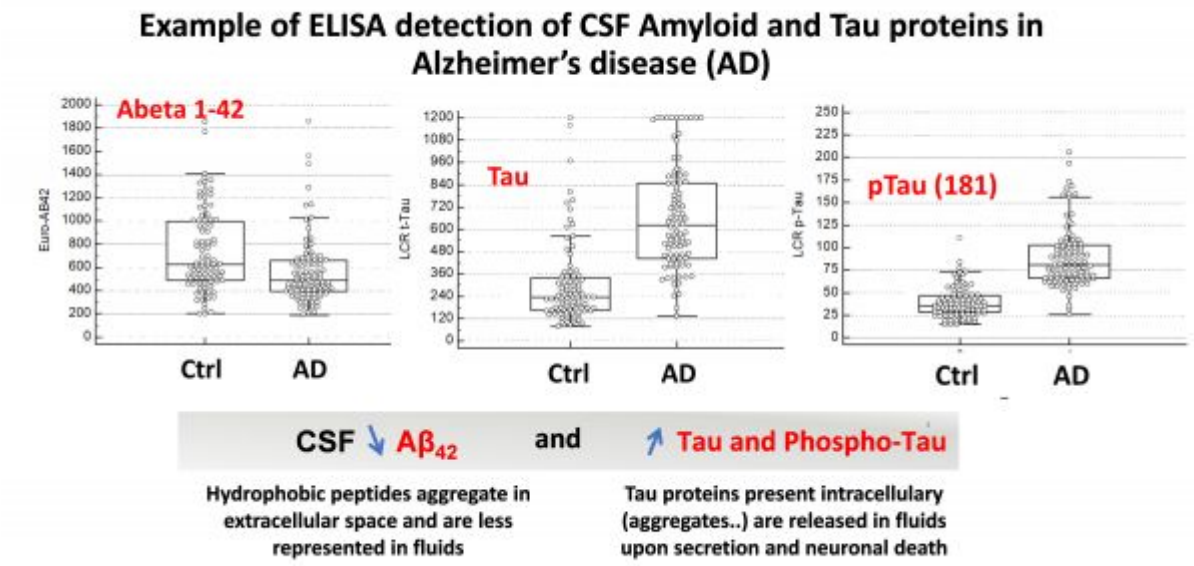
In presence of dementia, the first etiological investigation is to rule out using imaging (CT, MRI) and routine biology some secondary causes including, stroke, brain tumor, subdural hematoma, normal pressure hydrocephalus, neuronal consequences of infectious diseases (HIV, syphilis...), vitamin B12 deficiency or hypothyroidy. The main origin of dementia remains in fact neurodegenerative diseases, and in particular, in 2/3 of the cases, Alzheimer's disease (AD).

Biomarkers have recently taken an important place in the diagnosis and management of dementia. For genetic (familial) forms, diagnosis is mainly based on screening for genetic mutations responsible for the pathology in selected genes including: APP, PS1, PS2, tau, progranulin... However, AD is mainly sporadic and genetic analysis in this case could only identify the risk factor corresponding to the expression of the e4 allele of apolipoprotein E. The biomarkers that are the most important in nowadays and that are included in the AD diagnosis criteria are amyloid peptides (Aβ1-40, Aβ1-42) and tau proteins

(total tau and phosphorylated ptau(181)) in the cerebrospinal fluid (CSF) (see figure 1). These CSF biomarkers highlight the presence of histopathological lesions of AD: amyloid plaques and neurofibrillary tangles. They permit a diagnosis of AD in the very early stages of the disease (amyloid abnormalities being present probably 10 to 15 years before the onset of clinical symptoms). When CSF amyloid and tau biomarkers are indicative of AD, their combined sensitivity and specificity reached 90%. Importantly the only other neurodegenerative disease with routine diagnosis biomarkers is represented by Creutzfeldt-Jakob disease (CJD). In this case a very strong increase in tau, in the absence of a significant increase in ptau is observed. Detection of the 14-3-3 proteins in the CSF is also indicative of the disease and included in its diagnosis criteria.

Many other biomarkers in the CSF and in the blood have been proposed in the literature. It is impossible to be exhaustive on this subject. Moreover, many biomarkers have been proposed in small clinical studies, and need further validation. Other are truly differential but present an important overlap between diseases and controls, which impairs their use for diagnosis at an individual level. One biomarker, neurofilament light (NfL), is very interesting; not for the positive diagnosis of dementia, but rather as a prognosis biomarker. It is known for long time that NFl in the CSF is a good biomarker of neuronal damage, but what makes a real difference recently is the possibility to detect this biomarker also in the blood. It is therefore possible to use blood NFl to predict the evolution/severity of many dementia related diseases, including AD. Finally, one new approach for biomarkers that is also worth mentioning, is related to the amplified detection of aggregated proteins (prion, amyloid, tau, synuclein…) by real-time quaking induced conversion (RT-QuIC). This method that starts to be employed in routine for CJD, has a great potential for many diseases.

Keywords : Biomarkers, Neurodegenerative diseases, Alzheimer, CSF



Title: CSF AD biomarkers

Thursday, October 11th 2018

Hall A

16:30 - 17:30

S8.Endocrinologist And Laboratorian, A Friendship Under Construction

What Do The Endocrinologists Expect From Laboratory?

İlhan Satman[1]

[1]Institus for Public Health and Chronic Diseases (TUHKE)
[2]Health Institutes of Turkey (TUSEB)
[3]Istanbul University Medical Faculty, Div. Endocrinology and Metabolic Diseases

The practice of endocrinology relies heavily on accurate laboratory measurements. Small changes in hormone levels, biomarkers, or molecular markers are often more specific and earlier indicators of disease. Endocrinologists evaluate the results based on the reference range but overlaps make it hard to discriminate normal from abnormal. Also there is more than one range to allow for normal variations such as age, gender, menstrual cycle, menopause and pregnancy. Besides diagnosis of most endocrine diseases requires dynamic tests in which hormones are used for stimulatory or suppressing effects. Another issue is that the diurnal rhythm of several hormones, which can affect the blood level during the day and response to dynamic tests.

Analytic methods for assessing endocrine problems are continually expanding. Traditional measurement of endocrine factors, protein, and steroid hormones and related factors has been supplemented by a wide array of disease biomarkers. Many types of specimens are routinely used for the measurement of analytes in bodily fluids using whole blood, serum, plasma, urine, and saliva or aspirates. It is critical to understand that each type of specimen must be subjected to rigorous validation to ensure accurate measurements.

Regardless of the methodological sophistication, the most important step of the process is regular communication between clinicians and the clinical laboratory. Endocrinologists should be informed about the methods, their descriptions, and validation status. This will empower the clinician with insights into the inner workings of the laboratory systems and to encourage a more detailed level of interaction with the clinical laboratory.

The Role Of Laboratory In Metabolic Bone Disease

Howard Morris[1]

[1]University of South Australia

The clinical laboratory can play a critical role in the monitoring of treatment for metabolic bone disease. Assessment of vitamin D status can be a critical determinant of treatment and monitoring response to therapy. Biochemical bone markers of bone metabolism provide information on the current metabolism of bone cells which also may inform treatment and monitor response to therapy. The well characterised endocrine pathway of vitamin D metabolism and its activities are solely responsible for vitamin D regulation of plasma calcium and phosphate homeostasis under control of serum 1,25-dihydroxyvitamin D, the biologically active metabolite of vitamin D. This pathway protects against the metabolic bone disease of osteomalacia in adults or rickets in children. The critical level for serum 25-hydroxyvitamin D to maintain adequate serum 1,25-dihydroxyvitamin D is 20 nmol/L (8 ng/ml). In contrast a large body of data demonstrate that an adequate vitamin D status protects against osteoporosis, improving bone quality and reducing the risk of fracture. Bone cells metabolise 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D to elicit biological responses including osteoblast maturation, reducing bone resorption, and enhancing mineral retention in bone. Such actions protect bone quality and strength reducing the risk of fractures in

the elderly. The critical level for serum 25-hydroxyvitamin D for optimising the health of the skeleton is approximately 75 nmol/L (30 ng/ml).

Biochemical markers of bone turnover (BTM) have the theoretical potential for assessing two major clinical questions. Can baseline levels of BTM predict the rate of bone loss or future fracture risk? Can BTMs be used to monitor the response to treatments for osteoporosis? While assays for numerous BTMs are readily available on automated clinical analysers, there is no strong consensus on their clinical utility. There are significant associations between bone turnover markers and incident fracture risk, though these are modest. Studies on the use of BTMs for the monitoring of treatment have shown, in general, that the larger the decrease in BTM, the larger the reduction in fracture. Their clinical value is limited by inadequate appreciation of the sources of variability, by limited data for comparison of treatments using the same bone marker and inadequate quality control.

Thursday, October 11th 2018

Hall A

17:30 - 18:30

DEBATE

Hba1c Will Remain The Preferred Marker For Assessing Glycaemic Control

William Garry John[1]

[1]Norfolk and Norwich University Hospital

The argument in support of this statement is irrefutable; there is no other contender currently available that has the long history of development, investigation and clinical utility.

Glucose measurement formed the basis of diagnosing and monitoring diabetes, but this had several problems; results were affected by type of sample, food intake, time of day and year, and poor stability in the tube following collection. It was not surprising therefore that when Haemoglobin A1c (HbA1c) was first described 50 years ago it revolutionised clinical practice in relation to diabetes; and because of this HbA1c has been extensively studied.

What sets HbA1c apart from other glycaemic markers? HbA1c is now globally standardised with a network of reference laboratories and traceability of patient results to the primary reference material. No other glycaemic marker has this, not even glucose. Unlike fructosamine, HbA1c is a single molecular structure with a fully understood formation process which gives a clearly defined time period of control. Many clinical trials starting with the Diabetes Control and Complications Study have clearly shown HbA1c is directly related to outcome, and specific clinical targets for treatment have been defined and used successfully for decades. More recently with improved methodology and standardisation HbA1c is now reliably used to diagnose diabetes. No other glycaemic marker challenges this level of understanding; glycated albumin is a contender, albeit with a shorter life span, but evidence is sparse and many years will be needed to amass the evidence for it to replace HbA1c.

A potential challenger is continuous glucose monitoring (CGM); but there remain many problems, CGM meters mainly measure glucose in interstitial fluid and different meters utilise different collection sites. There is no standardisation and no traceability of results; until this is sorted there can be no agreement on target setting.

So will HbA1c will remain the preferred marker for assessing glycaemic control? There can be little doubt the answer is YES.

Keywords : Diabetes, Haemoglobin A1c, glycated haemoglobin

Hba1c Will Remain The Preferred Marker For Assessing Glycaemic Control

Eric S. Kilpatrick[1]
[1]Division of Clinical Biochemistry, Sidra Medicine, Doha, Qatar

The widespread use of HbA1c for assessing glycaemic control in patients with diabetes has been one of the most important developments in the management of diabetes since the discovery of insulin.

However, HbA1c is not for everyone. Globally, it is anticipated that the prevalence of diabetes will increase at its greatest rate in African, Middle and Far Eastern countries, where the presence of abnormal haemoglobins is common. It means that both this, as well as the test's cost, is likely to preclude its use in many of these new patients. There are other instances where HbA1c has limitations in pathological conditions, such as in renal disease, and also in physiological conditions such as pregnancy.

For these and many other situations, alternative markers of glycaemia are required. Venerable older tests such as inexpensive fructosamine, as well as newer markers such as glycated albumin (GA), have recently been found to be able to predict the microvascular complications of diabetes, so can now be used with complete confidence, either complementary to or instead of HbA1c. More recently again, the increasing availability of continuous glucose monitoring represents a way of directly calculating the mean blood glucose of a patient rather than using a surrogate like HbA1c. By allowing the additional assessment of glucose fluctuations it might therefore represent a real challenge to HbA1c measurement in affluent societies.

Keywords : Glycaemic control, HbA1c, fructosamine, glycated albümin

Thursday, October 11th 2018

Hall B

09:00 - 10:30

S22.Laboratory Testing Guideline In The Intensive Care Unit

The Role Of Laboratory Medicine In Intensive Care Unit (Beliz Bilgili)

Inflammation versus sepsis: Focus on biomarkers

Michael Meisner[1]
[1] Clinic of Anaesthesiology and Intensive Care Medicine

Despite the new Sepsis-3 definition, inflammation is a major part of sepsis syndrome. A variety of markers can be used for diagnosis of systemic inflammation, but still do not allow reliable differentiation of its etiology. Yet, every marker has a different profile and characteristics. Beside diagnosis of sepsis, guide of antibiotic therapy and assessment of therapeutic interventions by monitoring the severity of the systemic inflammatory response has impact on therapy as well. The problems of sepsis diagnosis of different characteristics of various sepsis markers and clinical usefulness and clinical consequences are presented.

Keywords : Inflammation versus sepsis: focus on biomarkers

TDM of antibiotics

Paul M. Tulkens[1]
[1]Louvain Drug Research Institute, Université catholique de Louvain (UCLouvain)

For many years, TDM of antibiotics has been limited to aminoglycosides and to vancomycin, mainly because of their known toxicities and of the availability of easy-to-implement commercial methods. Things have however changed dramatically over the last decade because of (i) concerns about efficacy of antibiotics in face of a general decrease of bacterial susceptibilities (MIC creeps and impact of efflux mechanisms); (ii) a better appreciation of the limits of antibiotics in relation to more severe (lower) breakpoints set forth by EUCAST (and also, but to a lesser extent, by CLSI); (iii) the development of new modes of administration such as continuous infusion making monitoring intrinsically easier to implement and dosing adjustment more readily achieved); (iv) a desire to optimize antibiotic dosing not only with respect to efficacy but also to prevention of the emergence of resistance; (v) and, lastly, the recognition of the critical impact of serum levels in relation to toxicities of more antibiotic classes (e.g. β-lactams, oxazolidinones) than originally considered as critical.

We will briefly summarize the main progresses made in these various directions, taking each time specific examples that show the interest of TDM in Intensive Care Units as well as in general wards. Thus, we will successively examine

- how efflux affects fluoroquinolones activities and MIC creep makes vancomycin less efficient, but how TDM has guided dosing adjustments that has restored efficacy (nosocomial pneumonia as an example);
- the impact of adopting lower breakpoints for the assessment of the activities of many antibiotics, taking β-lactams and macrolides vs. S. pneumoniae (community acquired pneumonia and exacerbations of chronic bronchitis) as an example;
- how vancomycin and β-lactam administration by continuous infusion can be implemented across a whole hospital and lead to a much more effective monitoring of their serum levels to better optimize their activity (all wards)
- how in vitro models allow defining how much the through concentration of β-lactams must stay above the MIC of the offending organisms to avoid the selection of less susceptible isolates and how to translate this information for actual TDM in patients at risk (Intensive Care Units);
- which pharmacokinetic parameters govern the onset of toxicities of oxazolidinones (focusing on thrombocytopenia) and of β-lactams (focusing on neurological toxicities) and how TDM can be used to minimize them (all wards).

Many of these developments still imply difficult-to-implement analytical techniques (such as LC-MS methods, requiring specialized instruments and skills) to avoid difficulties related to lack of sensitivity and specificity in patients who are often polymedicated and whose serum may contain abnormal metabolites (patients with impaired renal function, as an example). However, new, rapid methods coupled with computer-aided algorithms are in development to allow for point-of-care implementation.

Keywords : beta-lactams, vancomycin, lienzolid, continuous infusion, optimizatoin, resistance

Thursday, October 11th 2018

Hall B

13:00 - 14:30

S5.Detecting Kidney Disease: From Proteomics To The Clinical Laboratory

Urinary Exosomes As A Novel Source Of Biomarkers Of Kidney Disease

Elisabetta AM Verderio Edwards[1],Giulia Furini[1],David Boocock[1],Timothy S Johnson[2]

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Urine offers a direct readout from the diseased kidney, and as such is an excellent bio-fluid for chronic kidney disease (CKD) biomarkers. Despite this, studies analysing urine have been only partially successful due to a predominance of abundant plasma proteins that we know mask those originating from the cells lining the kidney tubules, which may better mirror disease progression. However, urine also contains nanosized vesicles (exosomes and ectosomes) released directly from kidney cells, which contain many low-abundance proteins that may be suitable CKD progression biomarkers. The talk will discuss the potential of urinary extracellular vesicles (uEV) to diagnose and monitor CKD progression.

In a pilot study we aimed to determine the feasibility of using uEV proteomics to distinguish between stable and progressive CKD. Exosomes and ectosomes were isolated from pools of urine samples from 20 patients with stable CKD (< 1.78 mL/min per year eGFR loss; average eGFR loss = - 0.17 mL/min per year) and 20 patients with progressive CKD (> 2.52 mL/min per year eGFR loss; average eGFR loss = 6.94 mL/min per year), along with 10 control subjects with no evidence of CKD. Tryptic peptides from uEV preparations were subjected to reverse-phase high-pressure liquid chromatography electrospray ionization tandem mass spectrometry (RP-HPLC-ESI-MS/MS) using a SCIEX TripleTOF 5600 mass spectrometer in data dependent acquisition mode.

486 proteins were identified in the exosomes of the pool of stable CKD patients and 581 in the exosomes of the pool of progressive CKD patients, of which 368 proteins overlapped. Therefore, 213 proteins were uniquely found in the progressive CKD patients' exosomes. Likewise, 254 proteins were found in the ectosomes of the pool of stable patients and 473 proteins were found in the ectosomes of the pool of progressive CKD patients, of which 207 overlapped, with 266 proteins uniquely found in the progressive CKD patients' ectosomes. uEV-free urines displayed 393 proteins in stable and 326 proteins in progressive CKD patients, but notably only 82 were unique in the progressive phenotype, indicating that exosomes offer a larger fingerprint of disease progression.

A qualitative comparison to identify enriched biological functions in uEV from the patients' pools with either stable or progressive CKD, using the Database for Annotation, Visualization, and Integrated Discovery (DAVID), showed several over-represented pathways in progressive uEV, of which the most significant consisted of small GTPase mediated signal transduction in both exosomes and ectosomes. Furthermore, exosomes (but not ectosomes) uniquely featured a pathway related to matrix remodelling (metallopeptidase Inhibitor 1 and matrix metalloproteinases) which is relevant to fibrosis progression underlying all forms of CKD.

Collectively these data from patients' pools with either stable or progressive CKD suggest that uEV derived from the kidney offer the potential for novel non-invasive biomarkers of CKD progression.

Keywords: Urinary Extracelluar Vescicles (uEV); Chronic Kidney Disease; Fibrosis progression; Biomarkers

Urinary Biomarkers In Kidney Transplantation: Application Of Mass Spectrometry To Measure Peptides And Proteins

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Kidney transplantation is the best therapeutic option for end-stage kidney disease and offers the best survival, quality of life, and cost-effectiveness compared with dialysis. Despite immunosuppression, allograft rejection remains a major contributor to graft loss. The early detection of the causes of renal graft dysfunction and graft loss is important. The role of non-invasive monitoring through biomarkers has been a subject of interest for many years. An assay that would detect early of graft injury through urinary biomarkers would provide advantages according to creatinine and graft biopsy.

Proteomic urine analysis could predict the diagnosis of renal transplant pathologies early. Urinary proteome includes the whole genomic protein content that is excreted in urine in health and disease conditions. The kidney proteome alone consists of approximately 4000 proteins, yet only a fraction has been functionally characterized. Similarly, more than 2000 proteins have been identified in the normal urinary proteome. In contrast to overt proteinuria, smaller genomic peptides and proteins ranging from 1 kDa to 20 kDa present in urine are not detected by usual biochemical tests in the clinical laboratory. Specific technologic approaches are utilized for their detection.

Mass spectrometry (MS) based proteomics offers the most comprehensive high throughput approach to identify protein composition. Several MS technologies have been developed in recent years; their analytical performance differs for reproducibility, dynamic range and limit of detection. Techniques for proteome analysis are of two types, gel-based (2-DE and 2D-DIGE) and gel-free [matrix-assisted laser desorption ionization (MALDI) and isobaric tags for relative and absolute quantitation (iTRAQ)]. Recently, methods that utilize instruments operating in parallel reaction monitoring modes, such as triple quadrupole and/or high-resolution accurate mass, have been developed and utilized.

Urinary proteome patterns in transplant patients could differentiate stable graft function from acute rejection (AR), urinary tract infection, acute tubular necrosis and calcineurin inhibitor toxicity. Most of the published studies have focused on the urine proteome, with identification of multiple molecules, although only a few have been reproduced by different groups, including uromodulin, beta 2-microglobulin and fragments of collagen. Several urine biomarkers have also been correlated with allograft injury, including CXCL9, CXCL10, CCL2, NGAL, IL-18, cystatin C, KIM-1. There are several important considerations when evaluating proteomic data and their interpretation; such as reliability of the protein/peptide identification, repeatability of the quantitative techniques, validation of the results. It is important to note that differing MS methods may influence the proteome signature and markers identified which may complicate its translation to the clinic. Rigorous technical and clinical validation studies are required to bring a novel biomarker from bench-to bedside.

Keywords : Urinary biomarkers in kidney transplantation: application of mass spectrometry to measure peptides and proteins

The Clinical Laboratory And Kidney Disease

Edmund J Lamb[1]

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The last decade or so witnessed a succession of national and international guidelines in both acute kidney injury (AKI) and chronic kidney disease (CKD), beginning with the publication of the United States' National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) in 2002 (1). The work of NKF K/DOQI was subsumed by Kidney Disease Improving Global Outcomes (KDIGO), who in 2013 published updated guidance on the identification, classification and management of kidney disease (2). Other national guidelines followed, including guidelines and recommendations in the AKI arena (3). These initiatives sparked intense interest in the standardisation of laboratory tests of kidney function. The focus of these efforts was on the mainstays of diagnosis; glomerular filtration rate (GFR) and proteinuria, but there has also been renewed interest in the search for newer and improved biomarkers. This presentation will review current issues and uncertainties in the laboratory contribution to management of kidney disease.

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Keywords : kidney, GFR, creatinine, cystatin C, albuminuria

Thursday ,October 11th 2018

Hall B

14:45 - 16:15

S14.Medical Guidelines And Clinical Decision Making

Medical Guidelines May Not Always Be Compatible With Laboratory Practice

Michel Langlois[1]

[1]University of Ghent

EFLM WG-Guidelines.

Medical guidelines on the use of in vitro diagnostic biomarkers are usually based on population studies that assessed the diagnostic performance of the biomarker (with a certain analytical method). However, these guidelines and the recommended cut-off values of the biomarker may not always be universally applicable, e.g., due to lack of standardization and between-method/between-laboratory variability. Often the recommended biomarkers are not completely validated according to essential criteria for medical use: analytical performance, clinical (diagnostic) performance, clinical- and cost-effectiveness. In the example of medical guidelines for cardiovascular disease prevention, LDL-cholesterol targeted strategies are based on population studies using the older precipitation methods and, therefore, not validated for use of the contemporary direct (homogeneous) assays.

Laboratory And Clinical Cooperation İn Enhancing Clinical Decision Making

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The task of laboratory specialists is not limited to generating test results, but includes advising on the clinical indications and choice of examinations, and interpretation of the results. The laboratory can support clinical decision making on several levels, from guideline development on a national level, to hospital protocols and result interpretation. The Dutch experience in guideline (GL) development and -implementation might illustrate the resent challenges that exist in the development and maintenance of clinical guidelines, including the role of laboratory medicine in this process. The first GLs were developed in the 70ties, and later developments included multi-disciplinary GLs, evidence based methods, and international cooperation. Other perspectives were included: patients' views and financial aspects. The latest developments are digital support in development, implementation and maintenance of GLs. GL development is expensive, with average costs of development and (major) revisions well above €100.000,-. Other policies are needed to keep this sustainable. New GLs have a modular format, with modules that can be updated separately and might be applicable in more than one GL. A major project has been started in The Netherlands to evaluate and revise all aspects of GL development and maintenance. This project includes most specialties, with laboratory medicine also taking part in this initiative. As has been shown before, laboratory aspects are not always sufficiently covered in clinical GLs (1). A solution might be the development of separate modules as part of clinical GLs, under the supervision of the laboratory specialty. Application of GLs and laboratory recommendations can also be improved by using requesting profiles, that have been developed for the most frequent indications in general practice. Interpretative commenting by laboratory specialist, e.g. in the evaluation of anaemia as recommended in a national GL, can further support clinical decision making.

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Keywords : clinical guidelines, decision support, guideline development

Demand Management (Test Utilization)

Ana-Maria Simundic[1]

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Test repertoire as well as test volume has dramatically increased over the last couple of decades. Such an increasing demand creates a pressure to the lab and wastes significant financial, material and human resources. Thus, laboratories are nowadays under an ever-increasing pressure to deliver more for less: more tests, more value and better quality with less staff, less money, less space, and within shorter time. Optimizing test utilization is an essential tool in achieving the above listed goals, improving patient safety and reducing the overall healthcare costs. Inappropriate test utilization means not only ordering a wrong test, but also not ordering a test which is necessary for a particular patient. Unfortunately, it has been already documented in the literature that many test results have never been looked at. This, of course raises many questions, one of them certainly is: where these tests necessary in the first place? Appropriate tests are those that lead to some clinical action or clinical decision and help the patient. Why doctors utilize tests inappropriately? The failure to either order an inappropriate test or not order an appropriate test occurs as a consequence of various reasons: ease of ordering tests and test availability, to learn something from the result, to just confirm a clinical opinion, due to insecurity or curiosity, patient, family or peer pressure, concern for liability (defensive medicine) and many others. The list is long and exhaustive. This lecture will provide an overview of the most common reasons for inappropriate test utilization, analyse ways to fight against it and give some practical examples of how this can be done.

Keywords : demand management, test utilization, inappropriate test, pre-analytical phase

Thursday, October 11th 2018

Hall B

16:30 - 17:30

The Rise And Fall Of Total Error Concept In Laboratory Medicine

Uncertainty Or Total Allowable Error: The Big Debate

Anders Kallner[1]

[1]Karolinska Institutet

All decisions and measurements are liable to an uncertainty, which is described by different, topic oriented concepts. Two components are usually identified: random – unintentional – variation i.e. precision and systematic – intentional – variation which is recognized as trueness. The debate deals with how these variations can be calculated and correctly and conveniently be expressed in one single expression.

Keywords : Uncertainty or total allowable error: The big debate

From Measurement To Diagnosis: Uncertainty In Laboratory Medicine

Elvar Theodorsson[1]

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Measurements in clinical chemistry rest on chemical structures or reactions ultimately visualised and quantified by measuring physical quantities. Chemical structures and reactions represent the major determinants of selectivity of measurements in clinical chemistry with the physical quantity playing a secondary role. Thorough understanding of the chemical structures and reactions involved is therefore essential in interpreting measurement results including interferences and matrix effects. Mathematical models are essential for calculating the concentration of a measurand in patient samples from results obtained when measuring reference materials/calibrators.
Amongst the fundamental novelties introduced in the third version of the international vocabulary of metrology (VIM3) is the understanding that conceptual- including mathematical models are also crucial for the understanding and practical implementation of metrology in all applied field including laboratory medicine. The concentration of the measurand is only indirectly reflected in the measured physical quantity value. Translating the quantity value to the result and to useful information is up to the laboratory and the user e.g. through the definition of the measurand and measurement- and diagnostic models used. The comprehensive *diagnostic model* includes the measurement model, including the calibration of the measurement system, knowledge and information about biological variation, diurnal variation, age and sex of the patient, the relevance of the "system"/sample taken, the sampling itself, sample transport and storage. Furthermore, it includes information about reference intervals, decision limits and other population and diagnosis – related information needed for the proper interpretation of the result.

The primary characteristics of successful manufacturing- and service industries is focus on customer needs, good relations and frequent contacts with customers and emphasis on innovation and development rather than documenting that what has always been done. The current strong and successful emphasis on preanalytical factors needs to be supplemented by work on postanalytical factors including interpretation of measurement results in proper clinical contexts. Major improvements in postanalysis are likely to use methods developed in the humanities including qualitative research methods, change management methods and tailored interventions. These improvements should optimally be driven by the laboratories that find an even higher purpose for their work by improved clinical diagnosis.

Measurements in laboratory medicine only matter when their results contribute substantially to increasing or decreasing the probability of diseases or to measure effects of treatments. Devoid of these contributions, the results “remain just numbers”.

Keywords : Metrology, postanalysis, uncertainty

Friday, October 12th 2018

Hall A

09:00 - 10:30

S11.A Harmonised Approach To Generating And Applying Biological Variation Data

Biological Variation, From Theory To Practice. The Projects Of EFLM

Sverre Sandberg[1],on behalf of the EFLM WG on biological variation and TG on biological variation database .[2]
[1]Norwegian Quality Improvement of Laboratory Examinations (Noklus) , Haraldsplass Deaconess Hospital, Bergen, Norway
[2]EFLM

Data from biological variation are used for many purposes, the most common are 1) to set analytical performance specifications, to generate reference intervals, 2) to calculate reference change values to judge the signifcance of changes in serial results of an individual and the probability that any change documented is clinical significant and 3) to calculate the index of individualities to be able to judge the importance of the reference interval. Data on biological variation has been of varying quality.

A working group (WG) and Task Group (TG) in EFLM consisting of more than 30 people have developed a critical appraisal check list to evaluate literature on biological variation and to extract essential information from the papers as well as summarise the information (Clin Chem 2018; 64: 501-14). The group has used this list to categorise biological variation papers as A, B, C and D depending on their methodological quality, with category A papers indicating high-quality and D poor quality. From each paper 22 items are extracted. Systematic reviews on biological variation for different groups of tests are under production. The WG has also collected data from about 100 healthy persons in 6 different European countries and is now generating new data for a lot of measurands (next lecture). One of the most important aims is to to deliver a database on the EFLM website with essential information about the biological variation and derived performance specifications for different measurands as well as the evidence behind the data.The database is under construction and will be launched in the near future

Keywords : biological variation, performance specifications, reference change value, EFLM

European Biological Variation Study (Eubıvas): Sample Collections From Healthy Volunteers From Six European Labs For Biological Variation Estimates’ Update

Anna Carobene[1]
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In recent years, concerns have been raised about the quality of the data available in published studies of biological variation (BV) as derived from publications employing obsolete analytical methods, or derived from studies with deficiencies in experimental design, where areas of concern include the pre-analytical and analytical phases of the experimental protocols employed and the data analysis [1].

The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) working group on BV has designed and implemented the European Biological Variation Study (EuBIVAS) [2, 3]. In the EuBIVAS, six European clinical labs in five different countries collected fasting blood samples for 10 consecutive weeks from 91 healthy volunteers. All samples, shipped on dry ice to the coordinating center in Milan, were stored at –80 °C until the analysis [2].

The opportunity to collect samples from healthy subjects from different countries was very attractive, but also hazardous because the possibility of introducing a significant pre-analytical variability, thus invalidating all the effort. To minimize this risk a very detailed protocol was prepared in agreement to the EFLM recommendations [4,5] and rigorously followed by each involved lab for all steps, and it has surely been the key for the success of EuBIVAS [6].

The mean values of the clinical chemistry EuBIVAS measurements performed until now are in fact perfectly overlapped and there is no data indicating any differences in pre-analytical variables between the labs. The only exception was serum creatinine in Turkey, but it is related to a real difference in the population [7]. Thus, the BV estimates obtained from EuBIVAS samples are widely applicable and can be used to determine analytical quality specification (APS) at an international level. All samples from each of the participants were analyzed in duplicate under standardized conditions. The resultant data sets underwent rigorous scrutiny and appropriate statistical analysis to enable delivery of BV estimates accompanied by CIs. So far, estimates for liver enzymes [8], for creatinine using enzymatic and alkaline picrate methods [7], for electrolytes, lipids, urea, uric acid, total protein, total and direct bilirubin, glucose [9], for prostate specific antigen [10], and for S100-b and neuron-specific enolase proteins [11], have been published. The main finding of the first step of EuBIVAS measurements is that most of within-subject BV (CV_I) and between-subject BV (CV_G) estimates [7-11] are lower than the corresponding estimates available in the on-line 2014 BV database [12], and, consequently, the APS derived from them. The second finding is that, for some measurands, significant differences between mean values in subgroups (i.e., males /females [7-9]; female menopause/fertile age [9]; or for creatinine Turkish people [7]) were found. When the mean value of a subgroup is significantly different from the other(s), the lowest CV_G from the different subgroups was used to calculate APS [7-9]. The next phase of the EuBIVAS, providing BV estimates for some coagulation routine tests, tumor markers, hormones and specific proteins, is under way. Thus, the EuBIVAS provides a valuable resource to enable delivery of high quality and well-characterized BV data for a large number of measurands, using a protocol that is fully compliant with the newly developed Biological Variation Data Critical Appraisal Checklist (BIVAC) [13].

Keywords: Biological Variation, Analytical Performance Specification, EuBIVAS

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Biological Variation Of CBC Tests: The Effect Of Turnarround Time

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Complete blood count (CBC) is one of the most informative group tests for the diagnosis and monitoring of various clinical situations such as infection, anemia and bleeding disorders. To enable clinical interpretation correctly, reliable data is needed on reference interval and biological variation (BV) of CBC parameters. Since the CBC tests are a heterogenous group and contain more than 20 different parameters, special attention is required to analyze the BV of these parameters to obtain reliable data.
For simplicity, classification of CBC tests can be in 3 subgroups: Erythrocyte and reticulocyte group, leukocyte group and platelet group parameters.

To obtain reliable data for BV studies of CBC parameters, strict pre-analytical protocol must be applied, and all subjects should be monitored during the period of the study (1). For example, subclinical infections such as mild flu may change the level of leukocyte group parameters which cause an artificial increasing of the BV of these group tests.

The turnover time of CBC parameters are not the same and therefore the length of the studies should be criticized before collecting samples, since the turnover of cell types might have significant effect on the BV of the CBC parameters. For example, the turnover of erythrocyte in circulation is approximately 4 months; whereas for platelets it is around 7–10 days. Therefore, in a study covering a 10-week period, each week a large part of new platelets will be measured but most of the measured erythrocytes will remain the same throughout the study. In a recent study the within subjects BV of platelets measured within 1 week and 5 weeks were shown to be different (2).

The between subjects BV of some parameters of erythrocyte and reticulocyte group in men and women might be different (1). Therefore, the data of men and women subjects should be evaluated separately to see the possible differences between genders.

All samples should be analyzed under the same conditions using standardized analytical techniques to avoid possible bias. The raw data obtained from the instruments should be evaluated in terms of outliers and suitable statistical techniques should be applied to refined data.

In conclusion the turnover time of cells and the gender of subjects might be crucial to obtaining reliable BV data of CBC parameters.

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Keywords : Biological Variation, Complete blood count, Turnover Time

Friday, October 12th 2018

Hall A

10:45 - 11:30

Plenary Lecture

The Liver: Maestro of metabolism

Nurdan Tozun

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The liver is a mysterious and laborious organ which fascinated people ,sorcerers and scientists for centuries.It was where the characters of the humans were read,the destinies were engraved and the future was predicted.The liver executes more than 500 functions by storing the energy, delivering fuel and nutrients to every single cell responsible for life, detoxifying noxious substances, producing hormones, protecting the body from the insults and accomplishing many other vital tasks.The liver is metabolically active and receives approximately 28% total body blood flow .It is a highly aerobic organ and extracts approximately 20% of O_2 used by body. The liver directs the synthesis and degradation of carbohydrates, proteins and lipids and regulates mineral and vitamin metabolism. When the liver fails the brain, the kidneys, the heart and many other organs fail. Briefly the liver is not only the site for hepatic diseases but also a mirror of pathologies in other organs. For example, C-reactive protein is an established marker of inflammatory reaction, whereas transferrin emerges as a liver stress marker and an attractive mortality predictor. Despite all these extremely important functions the liver is a silent and vulnerable organ. It is like a smoldering volcano which does not reflect the degree of the injury to the laboratory tests.i.e a compensated liver cirrhosis patient may have normal LFT; a chronic HBV patient may exhibit normal ALT and AST;severe lipemia can cause elevation in ALT, less elevation in AST but does not affect GGT**.** This fact makes the diagnosis of liver diseases even more difficult.The evolution of medicine from bedside diagnosis to laboratory medicine has made the clinical laboratory a true source of medical authority. The clinical laboratory serves as an amplifier to the physician's senses so that he can 'see', 'hear' and 'feel' at cellular, molecular and atomic levels. The lab, in one form or another, became nowadays an "obligatory passage point" for clinicians and researchers. This mandates a close collaboration between the clinician and the clinical biochemist in addition to optimized use of laboratory capabilities, the analytical and diagnostic performance of laboratory tests, hence the quality assurance. Since liver diseases may present with great variability of symptoms and signs the expectation of the physician from the laboratory is high especially in emergency conditions. Clinical utility of a lab test refers to its ability to differentiate between diseased and nondiseased persons .Due to the functional complexity of the liver, and because each test reflects a different component of liver function, one single liver function test cannot measure liver function comprehensively. The first questions asked by the clinician are: Does the patient has the disease and shall I treat this patient? What the clinician expects from the laboratory are: Information and clarity ,clinical validation (validation of cut-off values and diagnostic performances before ordering new tests), help to the rationale use of laboratory tests, rapid work up of tests and avoidance of sudden changes in results.To achieve these goals there is a need for: effective algorithms which will pave the way to right diagnostic tests at right time and in a cost-effective way, decentralized laboratories accredited by authorities, electronic recording, education and research. The laboratory biochemist also has some requirements such as sufficient information about the clinical state of the critical patient, correct sampling and optimal transport to the laboratory, accurate and up-to-date kits for test, adequate set up with good machines, adequate staff to endorse the work up, excellent information technology to speed communication and ensure data storage.What does a hepatologist expect from the

laboratory? To be warned about panic results as soon as possible, accurate and validated results, further tests when results are abnormal,collaboration between bench and bedside and availability of advanced techniques for difficult cases especially prior to liver surgery, before and after liver transplantation. A clinical diagnosis in liver diseases is most of the time a joint venture between the clinician and the laboratory physician, the microbiologist, the pathologist, the radiologist and many others. They should walk hand to hand in the difficult path of differential diagnosis of liver diseases and as our famous poet Tevfik Fikret said:" *The light of the truth emerges from the interaction and collision of ideas"*

Friday, October 12th 2018

Hall A

13:00 - 14:30

IATDMCT Symposium

The Future Of LC-MS/MS İn Forensic Laboratory And Clinical Toxicology

K. M. Rentsch

Laboratory Medicine, University Hospital Basel, Basel, Switzerland

LC-MS/MS

Liquid chromatography coupled to mass spectrometry (LC-MSMS) is nowadays an indispensable tool in the forensic laboratory and in clinical toxicology. It allows the identification of a very high number of compounds for confirmation of positive immunoassay results as well as the detection of yet unknown compounds present in an intoxicated patient without the need of an extensive extraction procedure and derivatisation. LC-MS/MS also allows the quantification of a high number of drugs and poisons with a short turn-around-time that is mainly important in clinical toxicology.

Ion traps and triple stage quadrupole instruments are less expensive and are therefore widely used in routine laboratories, whereas high-resolution instruments are mainly used in very specialized laboratories.

One of the difficulties of not using high-resolution instruments are the different mass spectra, which are gained by various instrument types and instruments of different manufacturers. In contrast to GC-MS there has yet no standardized ionization process been defined and the detection of the ions differs between different instruments. In addition, even mass spectrometers of the same type and manufacturer may have differences in the ionization performance due to the demanding manufacture process. For the clinical chemistry laboratory there are now fully automated LC-MS/MS instruments coming onto the market, which required at least for the instruments used in this devices to be more reproducible than before.

The most demanding analysis that has to be performed in the forensic laboratory and in clinical toxicology is the general unknown screening (GUS) or better the systematic toxicological analysis (STA). Due to the differences in the mass spectra generated by different instruments, the development of commercial libraries, which can be used on all instruments, is demanding. In contrast to GC where the analytical method is more or less defined by the temperature program, in LC different mobile phases can be applied having different pHs and composition. In addition, there are different ionization modes widely available, which generate different spectra.

The use of LC-MS/MS in forensic laboratory and in clinical toxicology will become more and more common and LC-MS/MS instruments will replace most probably the HPLC instruments coupled to UV or diode array detectors. In order to become a routine instrument all over the world the costs for the purchase must decrease and the robustness of the instruments must increase. In an optimal way, the different manufacturers should define a common standard for the ionization process. As an alternative, they should at least support the development and use of a software, which is capable to compare the actual spectrum with a library spectrum recorded on a different instrument with a high degree of certainty.

Therapeutic Drug Monitoring İn Transplant Patients

Eberhard Wieland[1]
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Modern immunosuppressive regimens have contributed considerably to the success of organ transplantation by reducing the acute rejection rates in the early phase after engraftment. Immunosuppressants (IS) require pharmacokinetic therapeutic drug monitoring (TDM) because of their narrow therapeutic index and significant variability in blood concentrations between individuals. TDM is widely practiced especially for cyclosporine, tacrolimus, everolimus, sirolimus, and mycophenolic acid. The accuracy and specificity of the drug measurements are fundamental to the clinical interpretation of the concentration data. Analytical methods that are used for TDM of immunosuppressive drugs must be precise and accurate to enable meaningful therapeutic decisions and dose adjustments. In addition, comparability of results between laboratories using different methods should be achieved as well as long term consistency of method performance and results because immunosuppression is a lifelong therapy in transplant patients. Commercial immunoassays and mass spectrometric kits are available but many laboratories still use laboratory developed in house technique, which are mainly based on tandem mass spectrometry (LC-MS/MS). In the recent years the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) has launched recommendations for the TDM of immunosuppressive drugs which meet current clinical needs.

Although pharmacokinetic TDM of IS aims to improve patient outcome, long term results of solid organ transplantation are not satisfactory. TDM guided immunosuppressive therapy cannot avoid under- or over-immunosuppression in individual patients because therapeutic ranges are a statistically derived surrogate for the action of IS drugs. Individualized immunosuppression is the ultimate goal to improve long term graft and patient survival. Therefore, biomarkers to diagnose organ damage and to predict clinical complications have been proposed to complement TDM. Several biomarkers have been identified either by assessing the specific pharmacodynamic (PD) effect of a particular drug or reflecting the immunosuppressive effect in general in a non-specific manner. The most promising candidates and the analytical requirements to measure these biomarkers have been also summarized in recent IATDMCT consensus documents.

The lecture will summarize the currently available IATDMCT recommendations for therapeutic drug management (TDM and biomarkers) in transplant patients.

Keywords: consensus documents, analytical performance, biomarkers, individualized immunosuppression

Therapeutic Drug Monitoring For Anti-Hypertensive Drugs

Erik van Maarseveen[1]

[1]University Medical Center Utrecht

Adherence to antihypertensive agents is of importance to attain blood pressure targets and thereby prevent short and long term cardiovascular events. Recently, LC-MS/MS technology has gained interest for compound screening in medication adherence assessment. Consequently, screening for antihypertensive agents in serum using LC-MS/MS in patients suffering from cardiovascular diseases is currently explored and has successfully been implemented as standard of care in various centers worldwide. The results of recent studies and data from clinical practice by our and other research groups show that screening and/or concentration monitoring of antihypertensive drugs with LC-MS/MS is a valuable tool for a detailed and objective assessment of adherence in patients suffering from cardiovascular diseases. This lecture will cover the clinical relevance of monitoring adherence to cardiovascular agents with LC-MS/MS, illustrated by results from recent studies and unpublished data. Next, bioanalytical and clinical challenges are addressed. Finally, implementation of adherence monitoring of cardiovascular drugs in clinical practice will be discussed.

Keywords : therapeutic drug monitoring antihypertensive cardiovascular hypertension mass spectrometry LCMSMS adherence compliance

Friday, October 12th 2018

Hall A

15:25 - 16:25

S18.Strategic Role Of Laboratory Management And Leadership In Clinical Outcome

The Role Of Laboratory Specialist In Clinical Diagnostic Team

Roberto Verna[1]**,Adriana Berumen Velazquez**[1]**,Michael Laposata**[1]

[1]World Association of Societies of Pathology and Laboratory Medicine; Sapienza University of Rome

A major challenge to most countries is the growing cost of healthcare. The cost of laboratory testing is approximately 3% of the total clinical costs. On the other hand, waste from inappropriate admissions to clinical departments is reported to be as high as 15%. A frequently used approach to save dollars in healthcare is the random reduction in the budget for laboratories, with a focus on reduction of the number of unnecessary laboratory tests. The World Health Assembly has approached the problem by publishing a list of essential in vitro diagnostic tests, in order to achieve a global rationalization of the problem.
A much more thoughtful strategy to saving healthcare finance is to improve the efficiency of the diagnostic process. This report presents an opportunity to reduce diagnostic error and increase the efficiency of diagnostic testing. Reduction in time to a correct diagnosis provides a major financial as well as a clinical benefit. In addition, reducing both overutilization and underutilization of laboratory tests while achieving the correct diagnosis is a major benefit to challenged healthcare budgets.

One approach taken to achieve major savings in healthcare has been the creation of "Diagnostic Management Teams," composed of experts in specialty areas of medicine who are primarily based in the clinical laboratory to advise physicians on the selection of only necessary tests and the interpretation of complex test results.

Keywords : Diagnosis, Diagnostic Error, Laboratory Medicine, Diagnostic Management Team

Laboratory Medicine In The New Regulatory And Healthcare Environment: From Essentialism To Consequentialism

Fatma Taneli[1]
[1]Department of Clinical Biochemistry, Manisa Celal Bayar University Faculty of Medicine, Manisa, Turkey

The goal of this presentation is to emphasize the role of the laboratory medicine specialist in participation to the multidisciplinary diagnosis team and inclusion of interpretive comments to the clinical biochemistry reports. The further importance of the laboratory medicine in improving patient outcomes will also be underlined in this new digital health era.

Laboratory leaders traditionally are focused on providing accurate, timely and cost effective test results. Co-ordination of patient care services, including laboratory information, is a high priority for patient safety. Appropriate test result interpretation starts with appropriate test orders. Patients have become more knowledgeable about their own health and well-being with access to the internet information. Patient safety and patient-based laboratory medicine is the ultimate healthcare policy.

Values of the medical tests are shifting from essentialism to consequentialism. In essentialism philosophy the value of the medical test was determined by the trueness of its results. However, in consequentialism philosophy, the value of the medical test is determined by the value of its consequences in healthcare.

Improving diagnosis can best be achieved by teamwork of multidisciplinary healthcare professionals such as internists, surgeons, pathologists, radiologist, laboratory medicine specialists and doctors from the relevant fields which can be summarized as multidisciplinary diagnostic team management. Diagnostic management team including experts synthesize the clinical and laboratory data and provide a concise interpretive report based upon medical evidence. Diagnostic team management changes the role of laboratory medicine is from specimen centered to patient centered; from clinical testing to clinical decision making; from laboratory performance to patient outcomes; and from provider of test results to partner of a patient care outcome. Diagnostic management team links laboratory testing to patient outcomes.

Innovations in digital health and the digitalization technology will have a great impact on future medical laboratory. It is obvious that the digital technology will transform the current medical laboratory by radical changes of emerging technologies, personalized medicine and patient autonomy. Both the laboratory medicine doctors and the patients will experience the digital health by use of easy access to medical records and the huge medical information of big data. In the near future routine laboratory medicine will use the electronic health records, patient access to the medical records, health apps on mobile phones, and the patients will encounter the use of wearable health technology. Laboratory medicine specialists must realize their changing role. In addition to their previous role as a laboratory results responsibility, their new roles such as consultation, medical interpretation of complex laboratory results and interacting both with physicians and patients will become increasingly important in improvement of patient care.

In the new healthcare environment no single medical specialist may perform the patient care all by itself but has to work in multidisciplinary teams to improve patient outcome. Our societies need to work to improve the curricula of training the laboratory specialists for their new roles in digital health. Laboratory scientists should be aware that they have the central position in the new digital health era.

Keywords : Diagnosis management team, patient outcome assessment, diagnostic errors, patient centered care, digital health

Friday, October 12th 2018

Hall A

16:40 - 18:10

S13.Autoimmunity, Allergic Disorders And Immunodeficiency

The Role Of The Laboratory In Diagnosis And Management Of Autoimmune Disease

Joanna Sheldon[1]
[1]University of London

Dr. Joanna Sheldon is a Consultant Clinical Scienitst in Immunology and Director of the Supraregional Protein Reference Unit at St. George's Hospital in London, part of South West London Pathology. The PRU is a NHS laboratory service receiving samples sent from all round the U.K. and the test repertoire covers allergy, autoimmune serology, CSF analysis, cytokines and monoclonal protein identification. Dr. Sheldon chairs the IFCC Committee on the Harmonisation of Autoantibody Testing that is currently working on preparation and validation of International Reference Materials for autoantibodies.

The global prevalence of autoimmune based diseases is estimate to be between 7.6 and 9.4%. The laboratory has a key role in supporting the clinicians to help diagnose and monitor these complex diseases. However, the detection and quantification of autoantibodies remain analytically fragile and laboratory scientists must develop a deep understanding of the limitations of autoantibody tests to guide clinicians in appropriate interpretation. Looking towards the future of greater automation and consolidation of tests onto single platforms, the laboratory scientists are ideally placed to investigate the causes of variation in autoantibody testing and to work alongside clinicians to better define patterns of autoantibodies that are associated with particular disease and disease phenotypes.

Keywords : The PRU is a NHS laboratory service receiving samples sent from all round the U.K. and the test repertoire covers allergy, autoimmune serology, CSF analysis, cytokines and monoclonal protein identification.

The Role Of The Laboratory In The Diagnosis And Management Of Allergic Disease (Ravishankar Sargur)

The Role Of The Immunology Laboratory In The Diagnosis And Management Of Primary Immune Deficiency (Kimberly Gilmour)

Friday, October 12th 2018

Hall B

09:00 - 10:30

S12.Role Of Gut Microbiota In Metabolism And Inflammatory Bowel Diseases

Gut Microbiota And Its Relationship With Obesity, Metabolic Syndrome And Diabetes

Ahmet Uygun
SBÜ Gülhane Education and Training Hospital

Diabetes is a group of metabolic disorders characterized by persistent hyperglycemia and has become a major public health concern. A combination of genetic and environmental factors contributes to the development of these diseases. Gut microbiota have emerged recently as an essential player in the development of obesity and diabetes. Altered gut microbiota have been strongly linked to disease in both rodent models and humans

Obesity is a major public health concern and has been rapidly spreading in both industrialized and the developing countries in the past few decades. Obesity increases the likelihood of chronic metabolic disorders, particularly insulin resistance, T2D, cardiovascular disease, fatty liver disease, hypercholesterolemia and a number of cancers.

Diabetes is a metabolic disorder characterized by hyperglycemia in the context of insulin-resistance, accounting for about 90% of all the patients worldwide with diabetes. T2D is strongly linked to genetic predisposition but also closely associated with obesity and insufficient physical activity. Recently, growing evidence has shown that gut microbiota play a critical role in the regulation of development of diabetes.

Both animal models and human studies have demonstrated a strong association between gut microbiota and host in health and disease. Growing evidence suggests that altered gut microbiota composition could play a causative role in the development of T1D, obesity and T2D;

Keywords : Gut microbiota; Type 1 diabetes; Type 2 diabetes; Obesity

Celiac Disease Antibody Testing: New Trends İn Diagnosis, Guidelines And New Markers

J. Stein
Frankfurt

Coeliac disease diagnostics have advanced considerably during the past decade owing to increased clinical awareness and improved tests. Previous diagnostic guidelines relied on histological analysis of duodenal biopsy samples. However, European and North American guidelines now recommend utilising symptoms, coeliac antibodies (primarily tissue transglutaminase 2 IgA and endomysial IgA antibodies), HLA determination and histological analysis of biopsy tissue for diagnosis. Some guidelines conclude that the diagnostic accuracy of tissue transglutaminase 2 IgA antibodies is sufficient to forego the evaluation of duodenal biopsies in certain children with very high antibody levels, provided they show a clear symptomatic response in addition to a positive endomysial antibody test and confirmation of genetic susceptibility. While monitoring of the gluten-free diet (GFD) is important, the available methods are insufficiently accurate to identify occasional gluten exposure that may cause intestinal mucosal damage. Serological tests are highly sensitive and specific for diagnosis, but do not predict recovery and are not useful for follow-up. Therefore, the detection of gluten immunogenic peptides (GIP) in faeces and urine have been proposed as new non-invasive biomarkers to detect gluten intake and verify GFD compliance in patients with coeliac disease.

Faecal Biomarkers In Diagnosis And Monitoring Of Inflammatory Bowel Disease (Murat Toruner)

Friday, October 12th 2018

Hall B

13:00 - 14:30

S17.Harmonisation Of Training And Continuing Professional Development In Laboratory Medicine

Curricula Of Laboratory Medicine In Medical Schools (Thomas Zima)

Standardization Of Education Of Specialists On Medical Biochemistry In Turkey

Pınar TUNCEL[1]
[1]Dokuz Eylül University Faculty of Medicine Department of Medical Biochemistry, İzmir Turkey

Medical biochemistry training in Turkey is carried out either by the University Medical Faculty Medical Biochemistry departments or by the Education and Research Hospital Clinical Biochemistry Units governed by the ministry of health. Duration of the training is 4 years and the legal authority responsible for the approval of the resident as a specialist is the Ministry of Health. Medical doctors and graduates of some non-medical disciplines (chemistry, biochemistry, pharmacy and veterinary science graduates) can enter residency programs, but all the graduates has to take a special entrance exam in order to begin their residency. Because of this variety of teaching centers and the residents, there was a need for the standardization of the residency programs. First efforts for the standardization of the training programs of medical biochemistry residency began in 2002. A commission worked on the curriculum of the medical biochemistry training program and a draft core education program was prepared. Then, during 2010 to 2014, 3 commissions were established consecutively and they prepared an outcome-based curriculum, which is approved and put into effect in 2016. The aim of the curriculum was defined as; to graduate specialists, who are able to discuss mechanisms in both health and disease conditions, have the knowledge to interpret the test results by integrating clinical and laboratory data, competent in managing a laboratory and have the responsibility for lifelong learning. Since the specialists should be a part of the medical team within the context of his/her own discipline and act as a bridge between the laboratory and the clinics, they have to work outside the laboratory during their training. To accomplish this aspect, during the last year of the training program 6 months of clinical rotation (4 months-internal medicine and 2 months-pediatrics) was defined. Besides clinical practice, there is also a one-month microbiology rotation in order to be acquainted with and learn the basic principles of a rather similar laboratory discipline.

Keywords: medical biochemistry training, curriculum development

Education Of Specialists On Laboratory Medicine In EU

Matthias Orth[1]
[1]Vinzenz von Paul Kliniken, Marienhospital, Institute for Laboratory Medicine, Stuttgart, Germany; Heidelberg University, Medical Faculty of Mannheim, Mannheim, Germany

The European Union has no administrative responsibility in healthcare. The European Commission's Directorate-General for Health and Consumers seeks to align national laws on the safety of food and other products, on consumers' rights and on the protection of people's health, to form EU wide laws. National laws, however, regulate healthcare exclusively, unlike to other fields where EU Legislation has to be obeyed in all EU countries.The situation becomes challenging when certain targets are adressed both by EU and by national legislation, such as cross-border healthcare services or free migration of European professionals.

Several processes are now well embedded in Laboratory Medicine to ensure quality and patient safety. Previously, the standardisation and harmonisation of methods and laboratory practices have been core

activities of the international and national societies for Laboratory Medicine. There is a similar view, that harmonisation can also be achieved for individuals working in medical laboratories and that voluntary technical standards developed to facilitate world trade (i.e. ISO norms) can be used. However, ISO standards do not assess clinical outcomes.

The patients' well-being is the primary focus of all procedures performed in healthcare such that, by implication, healthcare is different from trade. Specific ethical guidelines from the WMA regulate healthcare issues.

Changes in the perception of medicine as a vocation to that of a commodity are also calling into question the Medical Act, notably challenging the grey zone between qualified and nonqualified practitioners. Without doubt. some simple, brief and clearly defined processes of the Medical Act can be delegated and even substituted by non-physician professionals.

The relevance of the Medical Act in Clinical Pathology is particularly challenged by this. The personal contact between Clinical Pathologist and patients in most cases is indirect, nonetheless laboratory physicians play an important role in improving clinical outcomes for individual patients and there are legal issues which prohibit delegation of certain tasks to nonqualified practitioners.

By the statutory length of undergraduate and postgraduate training training, physicians in Laboratory Medicine are well placed to ensure provision of appropriate test repertoires, guiding test selection and thus ensuring cost-effective use of finite resources. Political pressures to use free movement of professionals across the EU to plug workforce shortfalls should not be used as an excuse to dilute the rigor of training.

Conclusions

Physicians in laboratory medicine do not practice in isolation. Instead a high-quality laboratory medicine service is critically dependent on the complementary roles of medical doctors, scientists and related laboratory personnel. Self-empowerment of patients, direct to consumer testing, free movement and internet technology currently challenge the established role of the laboratory-based physician and the standards included in the Medical Act, necessary to ensure the practice of high quality Laboratory Medicine. In the last few decades, the role of the physician in Laboratory Medicine has changed fundamentally to focus now on the diagnosis and management of disease, interacting with both physicians and patients. There is an urgent need for training curricula in Laboratory Medicine to reflect and support these changes in practice.

Keywords : postgraduate training graduate training, syllabus, physician in Laboratory Medicine, CME, patient empowerment, clinical pathology,

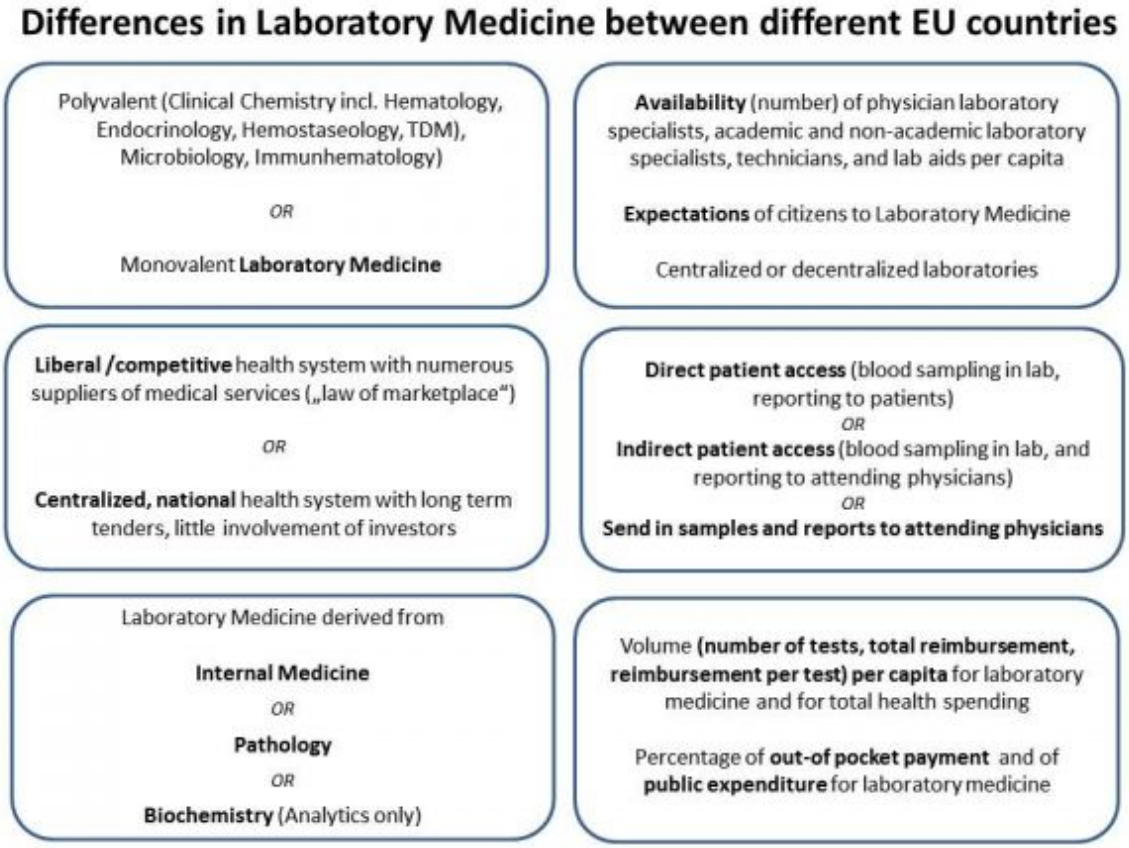

Figure Title: Heterogeneity of Laboratory Medicine among EU member states

Friday, October 12th 2018

Hall B

15:25 - 16:25

S1.The Role Of Clinical Laboratories In Diagnosis And Management Of Cancer

Therapy -resistant non-small cell lung carcinoma -The role of molecular tumor boards for clinical management(Leon van Kempen)

The Impact Of Flow Cytometry In Clinical Laboratory (Brent L. Wood)

Friday, October 12th 2018

Hall B

16:40 - 17:40

S9. Personalized Medicine

The Role Of Laboratory Medicine In Personalized And Precision Medicine

Mario Pazzagli[1],C. Di Resta Resta[1],C. Sipeky Sipeky[1],R. Van Schaik[1],I. Brandslung[1],P. Vermeersch[1],M. Schwab[1],J. J. Marc[1]

[1]Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy,[2]Vita-Salute San Raffaele University and Division of Genetics and Cell Biology, IRCCS San Raffaele Scientific Institute, Milan, Italy, [3]Institute of Biomedicine, University of Turku, Turku, Finland, [4]Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, The Netherlands, [5]Biochemistry Department, University of Southern Denmark and Vejle Hospital, Vejle, Denmark, [6]Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium, [7]Department of Pharmacy and Biochemistry, University of Tuebingen, Tuebingen, Germany, [8]Faculty of Pharmacy, University of Ljubljana, Askerceva 7, 1000 Ljubljana, Slovenia.

In contrast to population-based medical decision making, which emphasizes the use of evidence-based treatment strategies for groups of patients, personalized medicine is based on optimizing treatment at the level of the individual patient. The creation of molecular profiles of individual patients was made possible by the advent of "omics" technologies, based on high throughput instrumental techniques in combination with biostatistics tools and artificial intelligence. The goal of personalized laboratory medicine is to use advanced technologies in the process of preventive, curative or palliative patient management. Personalized medicine does not rely on changes in concentration of a single molecular marker to make a therapeutic decision, but rather on changes of a profile of markers characterizing an individual patient's status, taking into account not only the expected response to treatment of the disease but also the expected response of the patient. Such medical approach promises a more effective diagnostics with more effective and safer treatment, as well as faster recovery and restoration of health and improved cost effectiveness. The laboratory medicine profession is aware of its key role in personalized medicine, but to empower the laboratories, at least an enhancement in cooperation between disciplines within laboratory medicine will be necessary. Examples of successful use of molecular profiles in oncology and pharmacogenomics will be presented and the need of changes on the organization of the medical laboratory profession will be discussed.

Keywords : The role of laboratory medicine in personalized and precision medicine

Personalized Reference Intervals

Yesim Ozarda[1]

[1]Uludag University School of Medicine, Department of Biochemistry

Population-based reference intervals (RIs) are ideally derived from the reference population value distribution, usually the central 95% interval. The utility of population-based RIs is related to the ratio of within to between subject biological variability (index of individuality;II). When intra-individual variability is much lower than inter-individual variability (II is below 0.6), population-based RIs lose their usefulness. However, by partitioning RIs according to gender, age, etc., the II can be increased above 1.4 (1).

Knowledge of major sources of variation of biological quantities is a part of the concept of reference values. There are many analytes that are affected by biological characteristics, such as age, gender, or pregnancy, or by factors, such as season or geographic location. Certain quantities have predictable cyclical biological variation (daily, monthly, seasonal) and the knowledge of the expected values

throughout the cycle is certainly vital for clinical interpretation of laboratory data (2). When individuality still provides an indisputable argument, the use of subject-based RIs is far better than population-based RIs in monitoring individuals. Variations in the concentration of the analyte still within the RI can be significantly outside the subject's usual values, in which case it is useful to calculate if the reference change value (RCV) has been surpassed or to calculate the statistical significance of a trend. The graphical representation of the data in a linear fashion can be extremely effective in identifying trends even without any statistical evaluation. Such a visual reference should provide an indication that not all abnormal test results are "abnormal" and not all normal test results are "normal." Most clinicians have ignored the variability inherent in the measurement itself. Any test result is a product of biological variability, the analytical bias, and the analytical imprecision, i.e., the reported result is actually a sub-range of values within and/or outside the continuum of the RI. Fraser et al. have effectively applied these principles into the concept of reporting the RCV (3). Reporting RCV should get us a little closer to the concept of "individuality" for each measurand's variability and the understanding that many test results should not be evaluated only against population-based RIs, but also against the individual patient's homeostatic thresholds. However, it should be considered that biological variability is not always identical in diseased and non-diseased subjects and RCVs established during health may be inappropriate for use in monitoring sick patients.

While personalized medicine is escalating and becoming more common, CLSI, EP28-A3c Guideline (4) mainly deals with population-based RIs and does not address the issue of individual RIs. However, the IFCC, Committee on Reference Intervals and Decision Limits workplan should include this important issue and add the definitions, explanations and recommendations for the estimation and best use of personalized RIs to the guideline. This symposium will explore these issues and provide those attending with some insight into the complexities of common areas of practice for personalized RIs.

1. Sikaris K.Clin Biochem Rev 2014;35;3-10.
2. Ozarda Y.Biochem Med 2016;26;5-16.
3. Fraser C. Clin Chem Lab Med 2001;50:807-812.
4. CLSI, EP28-A3c. Defining, Establishing and Verifying Reference Intervals in Clinical Laboratory; Approved Guideline 2010.

Keywords : Reference intervals, individuality, reference change values

Saturday, October 13th 2018

Hall A

09:00 - 10:30

S20. Patient Safety And Ethical Issues In Laboratory Medicine

Improvement Of Laboratory Test Value By Evidence Based Strategies

Mustafa Serteser[1]

[1]Acibadem Mehmet Ali Aydinlar University, School of Medicine

In recent years, changes in the the landscape of healthcare resulted into consolidated regional networks providing sophisticated medical care whereas generalized medical care remined in satellite sites. Same transformation has been observed in diagnostic laboratories too. Reference diagnostic centers are providing more complicated but non-urgent tests and the hospital laboratories provide emergent parameters together with routine ones. Point-of-care testing has widespread coverage not only in outpatient clinics or in-home testing but also in physician offices and even in retail clinics in many western countries recently.

Cost-containment is being demanded by payers continuously. Now it's clear that, providing diagnostic tests in efficient quality boundaries in clinical laboratories is not enough and value of tests are requested to be known.

Spesific challenges emerge for clinical laboratories: leadership and team building for establishment of the role of clinical laboratories in disease management and value added laboratory services for care givers together with clinical consultation with physicians. Performing cost analysis of laboratory operations also gains importance.

The future strategies of clinical laboratories will be discussed in terms of value added laboratory service creation.

Keywords: laboratory medicine, leadership, clinical consultation, cost containment

Ethical Issues In Laboratory Medicine (John Harris)

Saturday, October 13th 2018

Hall A

10:45 - 11:30

Plenary Lecture

Patient Focused Laboratory Medicine

George David Lundberg[1]
[1]Stanford University

The author will tell a story about a tragic case of a single mishandled laboratory test that lead to the death of a young American man in Los Angeles.

By analyzing the root causes of this system error and implementing corrective actions, the entire field of patient-focused laboratory medicine/management came into existence. Panic (or Critical) Values were invented, as was the concept of a vital 9 (now 10) point Brain to Brain loop of a laboratory test. Pre and Post Analytic Laboratory safety factors and actions needed to prevent the errors that result from failure to assess, monitor, control and assure the integrity of each step were defined with continung evolution towards a "more perfect" system.

References:

1. Lundberg GD. Acting on significant laboratory results. JAMA 1981; 245:762

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3. Lundberg GD. Adding outcome as the 10th step in the brain to brain laboratory test loop. Am J Clin Path 2014; 141: 767-769

4. Lundberg GD. Managing the Patient Focused Laboratory, Medical Economics Publshng Company, Oradell, NJ, 1974

Keywords : patient, critical values, panic values, quality assurance, brain to brain loop, pre and post analytic, errors, outcomes

Saturday, October 13th 2018

Hall A

11:45-12:45

S6. Diet, Inflammation And Atherosclerosis

Vascular Inflammation And Atherosclerosis

Burcu Barutcuoglu[1]

[1]Ege University; School of Medicine, Department of Clinical Biochemistry

Atherosclerosis is a dynamic and progressive disease arising from vascular endothelial injury, also known as endothelial dysfunction and an inflammatory response to that injury. Vascular endothelium has several crucial functions like coagulation, fibrinolysis, vascular tone, growth and immune response. Vascular homeostasis is maintained by a balance between endothelium derived relaxing and contracting factors. Endothelial dysfunction is the loss of any of the maintenance of vascular homeostasis. Risk factors such as dyslipidemia, obesity, diabetes mellitus mediate endothelial dysfunction which result in increased susceptibility of the vasculature to atheroma formation. Endothelial dysfunction promotes inflammation which leads to sequence of events within the vessel wall; atherosclerotic lesion initiation and progression and complications. Atherosclerosis is a disease characterized by low-level vascular inflammation. Initiation of inflammatory response increases the expression of adhesion molecules and chemoattractants which promote adherence of cells like platelets, monocytes to endothelium. Activated platelets release cytokines and growth factors by their granules. Cytokines, growth factors and also thrombin, all contribute to the migration and proliferation of smooth muscle cells and monocytes, formation of thromboxane A_2, a potent vasoconstricting and platelet aggregating substance, or leukotrienes, which increase inflammatory response. Proinflammatory cytokines, acute phase proteins like C-reactive protein (CRP), oxidized low density lipoprotein(OxLDL) uptake via lectin-like oxLDL receptor-1 (LOX-1), CD40/CD40 ligand interactions induce the expression of adhesion molecules. The adhered monocytes to the endothelium migrate across and within the arterial intima, the monocytes develop into macrophages and begin to express scavenger receptors such as Scavenger receptor A(SR-A), which internalize the modified lipoproteins. Accumulation of lipid laden macrophages, known as foam cells are the characteristics of early atherosclerotic lesions. These foam cells secrete proinflammatory cytokines which provide chemotactic stimulus for adherent leukocytes, increase SR-A expression and promote more macrophage accumulation. Release of the inflammatory response molecules by the activated T-cells, endothelial cells and foam cells increase inflammation, lipid accumulation within the atheroma and smooth muscle cell activity. Activation of inflammatory cells lead to the release of hydrolytic enzymes, cytokines, chemokines, and growth factors, which can induce further damage and as a result lead to focal necrosis. The predictive value of many markers of vascular inflammation such as C-reactive protein (CRP), adhesion molecules, cytokines and chemokines and leukocyte activation markers have been investigated in atherosclerotic patients. CRP is an acute phase protein and an inflammatory marker secreted in response to the increase of interleukin-1, interleukin-6, and tumor necrosis factor alpha(TNF-α). CRP is mainly synthesized by the liver and also by cells in atherosclerotic plaques. CRP can be generated within the plaque and reflects the intensity of vascular inflammation. High-sensitivity CRP (hsCRP) assay is widely used to predict cardiovascular events in atherosclerotic patients. Proatherogenic cytokines such as IL-6, IL-17, interferon-ɣ, TNF- α are novel diagnostic biomarkers and strong targets of atherosclerotic patient's treatment.

Keywords : atherosclerosis, vascular inflammation

Metabolomics And Cardiovascular Disease

Matthias Nauck[1]
[1]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald

The term metabolome covers the comprehensive determination of the small molecule content of various biomaterials, e.g. blood, urine or tissue. Main advantages of ^{1}H-NMR spectroscopy comprise its high reproducibility and minimal sample preparation. Furthermore, using only one internal standard enables quantification of metabolite concentrations. It is well-established, that Diabetes mellitus and the metabolic syndrome are related to cardiovascular disease. We are now able to determine lipoprotein subfractions in an easy and reliable manner using ^{1}H-NMR spectroscopy. These data allow to assess the cardiovascular risk in a superior manner compared to the informative value of LDL-cholesterol alone. In summary, NMR-based metabolomics has a great potential to derive novel biomarkers as well as to improve our understanding of the underlying pathophysiology.

Keywords : Metabolomics and cardiovascular disease

Saturday, October 13th 2018

Hall B

09:00 - 10:30

S21. Smart Technologies In The Diagnosis And Monitoring Of Patients

Lab-On-A-Chip

Yıldız Uludağ[1]
[1]UEKAE - BILGEM - The Scientific and Technological Research Council of Turkey (TUBITAK), 41470 Gebze/Kocaeli, Turkey

The biosensor market is dominated by glucose sensors for years, not only due to the high number of diabetes people who require blood glucose detection daily, but also detection can be achieved fairly simply by just adding a prick of blood on to an enzyme immobilized sensor chip. Whereas for tests such as pathogen detection or disease biomarker detection, immunoassay or DNA based complex assays are required, where the biosensor device need to have sensor integrated microfluidic system containing microchannels, microvalves, micropumps, miniaturized transducers with simple user interface for ease of use.

Due to the advances in lab-on-chip technology, nanotechnology and microfluidics, in recent years we have started to see some fine examples of point of care devices for clinical diagnostics. While the high research and development cost of these devices can be seen as one of the weaknesses, in the age of internet of things (IoT), the ever increasing demand for sensors of personal care, wellness monitoring and point of care testing for rapid on site results pushes the researchers and engineers to develop novel devices for everyday use.

In this presentation we will have a snapshot of the current technologies used in the lab-on-chip based diagnostic devices and will look into the future trends.

Keywords : diagnostics, biosensors, lab-on-chip

Enhancing Precision Medicine Through Clinical Mass Spectrometry Platform

Dobrin Svinarov[1]
[1] Alexander University Hospital, Faculty of Medicine, Medical University of Sofia, Bulgaria

There is an extraordinary flood of new technologies in medicine nowadays - sophisticated diagnostics based on mass spectrometry, genome assays and cell sorting platforms are driving the technological transfer and promote the entrance of individualized patient management in clinical practice. Mass spectrometry (MS) could be viewed as one of the major tools that promote the development of precision medicine. Precision medicine (also referred to as personalized medicine), employs patient's genotype and phenotype investigation to establish individually tailored drug treatment. While genetic testing allows the physician to choose appropriate medicine, the performance of MS assays provides the patient's actual phenotype, with all of the environmental, pharmacological and pathological variables. Therefore, MS is essentially important technology for personalized patient management. GC-MS was the starting of MS for clinical analysis, and still remains a working horse for clinical toxicology. LC-MS/MS (QQQ) is the today's most utilized analytical platform, but high-resolution MS systems are also employed to resolve challenging analytical demands. The great technological advance of LC-MS/MS resulted in the introduction of methods with extreme sensitivity, specificity and extended linearity range, which are simpler to use in the medical laboratories, and are based on the current reference analytical principles. Further, the ability to perform panel profiling with simultaneous measurement of bioactive compounds, their precursors and metabolites in a single sample, enormously amplifies the informative value of results, with ultimate improvement of patient care. Typical examples include new born screening, TDM, toxicology, endocrinology and others. There is an ultimate demand for clear differentiation of the stages discovery, selection and validation of newer biomarkers, as well as analytical method development and validation of MS techniques that are standardized to meet criteria for clinical use with post validation routine proficiency testing assessment. CLSI has issued guidance for validation and performance characteristics of LC-MS/MS methods for clinical use. Currently, MS is the preferred technique in central laboratories, where the expertise and the larger sample workload provide cost-effectiveness and reliability in applications. Clinical MS will flourish in the near future, with the introduction of certified commercial LC-MS assay kits, and automated analytical platforms closely resembling routine clinical chemistry analyzers. In addition, clinical MS will meet and get together chemical and anatomical pathology, with ultimate impact on precision medicine.
Keywords: mass spectrometry, chemical pathology, anatomical pathology, precision medicine

MALDI Imaging In Clinical Laboratories

Ahmet Tarık Baykal[1]
[1]Acıbadem Hospital

MALDI-Mass Spectrometry based imaging studies is gaining more interest as the instrument resolution, speed and sensitivity increases. Those are the most important aspects of tissue imaging studies with a mass spectrometer. MALDI-IMS provides spatial information that was lost during LC-MSMS based protein expression analsis or metabolomics experiments. The spatial information regarding the changes in the levels of molecules like protein, peptide, metabolites, lipids, and drugs provides an in dept knowledge on the molecular mechanisms, possible biomarkers that might be clinically useful . Combining the high chemical resolution of MALDI-IMS and the high spatial resolution of microscopy will enable ground breaking research as the tools necessary to compute the data generated.
Keywords : MALDI-Mass Spectrometry based imaging studies is gaining more interest as the instrument resolution, speed and sensitivity increases

Saturday, October 13th 2018

Hall B

11:45-12:45

S2. Biomarkers Of Heart Failure And Prognosis

The Utility Of High Sensitive Troponins In Early Diagnosis Or Rule Out Of AMI (Mehmet Ağırbaşlı)

Prognostic Markers Of Heart Failure

Mehmet Birhan YILMAZ[1]
[1]Cumhuriyet University

Heart failure is a disease of 21st century with a high mortality and morbidity. Incidence is rising along with hospitalization burden and it becomes one of the most important health issue, particularly of aging population. In order to stratify the different phenotypes, modify the disease, tailor the therapy, several biomarkers among which natriuretic peptides remain the cornerstone, are introduced to the literature. Natriuretic peptides are semiquantitative biomarkers of the heart and hence reflects the loading conditions of the both chambers. Hence, they can prognostically estimate the status of the patient. On the other hand, there are other biomarkers, such as ST2, galectin, GDF-15, CA-125 and along with different pathways, they bring about the chance to further predict the prognosis of the HF patient. Herein, within the light of recent guidelines and the literature, prognostic markers of heart failure will be discussed.
Keywords : heart failure, prognosis, biomarker