

The Association of Clinical Biochemists in Ireland

Annual Conference 2011

34th Annual Conference

14 & 15 October 2011

Hilton Hotel - Charlemont Place



www.acbi.ie



ACBI

Annual Conference 2011

Proceedings of the 34th Conference of the
Association of Clinical Biochemists in Ireland

14th and 15th October

Hilton Hotel,
Charlemont Place, Dublin 2

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Organising Committee

ACBI 2011:

Ms. Eileen Byrne, Dr. Sean Cunningham, Professor Joe Duffy,
Ms. Orla Maguire, Mr. Rowland Reece, Mr. Dermot Deverell,
Mrs. Lindsay Bond O'Neill, Mrs. Frances Sherry.



Table of Contents

4	From the President of the ACBI
5	Continuing Education
6	Welcome to ACBI 2011
8	Programme
12	Session 1
13	Chair and Speaker Biographies
14	Dr. Barry White
15	Dr. Mario Plebani
16	Dr. Gifford Batstone
18	Session 2
19	Chair and Speaker Biographies
20	Dr. Paul Collinson
21	Prof. Ken McDonald
22	Dr. Paul Collinson
24	Session 3
25	Chair and Speaker Biographies
26	Prof. Charles Gallagher
27	Prof. Philip Mayne
28	Dr. Edward McKone
30	Session 4
31	Chair and Speaker Biographies
32	Dr. John Plevris
33	Prof. Munir Pirmohamed
34	Prof. Aiden McCormick
36	Poster Presentations
37	Poster Index
42	Poster Abstracts



A message from the President of ACBI

On behalf of the Association of Clinical Biochemists in Ireland (ACBI), I am delighted to welcome delegates to the 34th Annual Conference of the Association. The conference is again being held in the Hilton Hotel, a venue which has proved popular with delegates due to its proximity to Dublin city centre.

This year's conference will focus on Cystic Fibrosis, Cardiac and Liver Disease and aims to provide delegates with up-to-date information on the diagnosis, monitoring and treatment of patients with these conditions. In addition, the opening session entitled Laboratory Medicine – the Wider Context deals with various aspects of the provision of laboratory services and will no doubt equip delegates with the knowledge to ensure the optimal delivery of services in improving patient care.

Apart from the formal Scientific programme, there is an opportunity for delegates to present their own work in the form of Poster Presentations and share their knowledge with their colleagues. The Geraldine Roberts Medal will be awarded to the author of the best scientific Poster at the conference.

'Labs are Vital Ireland' are in the process of rebranding into a new initiative called 'Analysis in Action' and details of this

development will be presented at the conference. The new focus will build on the excellent track record of 'Labs are Vital' and continue to raise awareness and understanding of the role and contribution of clinical laboratories to healthcare.

I would like to take this opportunity to thank our corporate colleagues in the diagnostic industry for their generous support which has contributed, in no small part, to the enviable reputation that ACBI conferences continue to enjoy.

Finally, I would like to congratulate Frances Sherry (Chair of the conference committee) and the other members of the committee in St. Vincent's University Hospital on organising such an exciting and wide-ranging programme. I have no doubt that it will prove, as previous ACBI conferences have, to be an enjoyable event and a valued source of knowledge on the use of biochemical testing in the provision of healthcare.

Orla Maguire
President, ACBI



Continuing Education

The Royal College:

ACBI 2011 has been approved for CPD by the Royal College of Pathologists (RCPATH).

Clinical Biochemists and Medical Staff in career grade posts, who are enrolled with the Royal College of Pathologists for CPD purposes and attend the meeting, will be entitled to receive CPD credits.

CPD: Maximum 9 credits for the two day meeting.

In order to receive these credits, the participant must sign the RCPATH register for each day attended and is issued a certificate of attendance by the conference organising committee.

Academy of Medical Laboratory Sciences:

ACBI 2011 has been approved by the Academy of Medical Laboratory Sciences (AMLS) for the award of CPEP points. A total of 15 CPEP points will be awarded for attending both days.

Online registration is now available to AMLS members and a password will be displayed on screen at the end of each day's conference. Therefore, members do not need to sign for these points at the actual conference this year. Each member is issued a certificate of attendance by the conference organising committee.

Evaluation of ACBI 2011:

All conference participants are requested to complete the conference evaluation form located in delegate bags. This form is to be returned to the conference registration desk. The ACBI uses this form to evaluate the quality and educational benefits of its meetings in order to maintain a tradition of high educational standards. This process also assists in the planning of future events.

Welcome to ACBI 2011

On behalf of the organising committee, I would like to welcome you to the 34th annual conference of the Association of Clinical Biochemists in Ireland.

The organising committee is based in St. Vincent's University Hospital again this year and we are returning to the Hilton Hotel, Charlemont Place, Dublin 2. Its central location and excellent service was very popular last year so we hope to repeat that performance this year.

This year, the conference will focus on Laboratory Medicine, Cardiology, Cystic Fibrosis and Liver Disease. We are delighted to welcome both national and international experts in each of these areas and we hope to generate lively discussions and provide an opportunity for the exchange of information and ideas.

I would like to take this opportunity to welcome our corporate delegates. The association is always very grateful for their continued generous support without which this conference would not be possible.

Finally, I would like to thank our conference co-ordinator, Lindsay Bond O'Neill, for her tireless enthusiasm, hard work and dedication. I would also like to thank our webmaster, Dermot Deverell, for his extensive support and diligence and our scientific committee for their help and valuable contribution to this event.

Frances Sherry
Conference Chairperson





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Programme - Friday 14th October 2011

8.45am:

Tea and coffee

9.15am:

Opening Comments: Ms. Orla Maguire, President of the ACBI

9.30am:

Official Opening Address: Dr. James Reilly TD, Minister for Health

SESSION 1: LABORATORY MEDICINE – THE WIDER CONTEXT

Sponsored by: Biomnis Ireland

Chairperson: Dr. John O'Mullane,
Cork University Hospital



9.50am-10.30am:

Clinical Strategy and Programmes

Dr. Barry White,
National Director for Clinical Strategy and Programmes,
Dr. Steevens' Hospital, Dublin

10.30am-11.00am:

Tea and coffee

Poster presentation viewing

Authors of posters 1 - 7 in attendance

Sponsored by: Aalto Bio Reagents



11.00am-11.40am:

Errors in Laboratory Medicine and Patient Safety

Dr. Mario Plebani,
Department of Laboratory Medicine, University Hospital, Padova, Italy

11.40am-12.20pm:

Standardisation of LIS connectivity - National Laboratory Medicine Catalogue

Dr. Gifford Batstone,
Clinical Lead for Pathology, DH Informatics Directorate, NHS

12.20pm-12.30pm:

Analysis in Action (formerly known as Labs are Vital)

12.30pm-2.00pm:

Lunch & Poster presentation viewing

Authors of posters 8 - 15 in attendance 1.30pm - 2.00pm



Programme - Friday 14th October 2011

SESSION 2: CARDIOLOGY AND BIOCHEMICAL MARKERS OF HEART DISEASE

Sponsored by: Sarstedt Ireland

Chairperson: Dr. Sean Cunningham,
St. Vincent's University Hospital, Dublin



2.00pm-2.40pm: High Sensitivity Troponin and the pain to come

Dr. Paul Collinson,
St. George's Hospital, London

2.40pm-3.20pm: Heart Failure – Diagnosis and Management

Prof. Ken McDonald,
Heart Failure Unit, St. Vincent's Healthcare Group

3.20pm-3.50pm: Tea and coffee

3.50pm-4.30pm: Novel biomarkers – fact or fantasy

Dr. Paul Collinson,
St. George's Hospital, London

4.30pm: Close of session

4.45pm-5.45pm: ACBI Annual General Meeting

**7.00pm: Sparkling Reception
and**

Conference Dinner

Hilton Hotel, Charlemont Place, Dublin 2.

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Programme - Saturday 15th October 2011

SESSION 3: CYSTIC FIBROSIS

Chairperson: Ms. Deirdre Deverell,
Children's University Hospital, Temple St., Dublin.

9.30am:

Tea and coffee

10.00am-10.40am:

Cystic Fibrosis - an Evolving Disease of Middle Age and the Elderly

Prof. Charles Gallagher,
National Referral Centre for Adult Cystic Fibrosis,
St. Vincent's University Hospital, Dublin

10.40am-11.10am:

Tea and coffee

Poster presentation viewing

Authors of posters 16 - 20 in attendance

11.10am-11.50am:

Screening For and Diagnosis of Cystic Fibrosis

Prof. Philip Mayne,
Children's University Hospital, Temple Street,
Our Lady's Children's Hospital, Crumlin and the Rotunda Hospital

11.50am-12.30pm:

The Genetics of Cystic Fibrosis

Dr. Edward McKone,
St. Vincent's University Hospital, Dublin

12.30pm-2.00pm:

Lunch



Programme - Saturday 15th October 2011

SESSION 4: LIVER DISEASE

**Sponsored by: BD Diagnostics -
Preanalytical Systems**

Chairperson: Dr. Damian Griffin,
University College Hospital, Galway



2.00pm-2.40pm: Aspects of Liver Disease: Fatty Liver and Liver Fibrosis

Dr. John Plevris,
Royal Infirmary of Edinburgh

2.40pm-3.20pm: Drug Induced Liver Injury

Prof. Munir Pirmohamed,
University of Liverpool

3.20pm-3.30pm: Presentation of Geraldine Roberts Medal

3.30pm-4.10pm: Liver Transplantation

Prof. Aiden McCormick,
St Vincent's University Hospital, Dublin

4.10pm: Close of conference

SESSION 1

Laboratory Medicine – the wider context



Sponsored by Biomnis Ireland

Chair

Chairperson: Dr. John O'Mullane, Cork University Hospital.

Speakers

Dr. Barry White

Clinical Strategy and Programmes

Dr White is on secondment from St James's Hospital, Dublin 8, where he is a Consultant Haematologist and Director of the National Centre for Hereditary Coagulation Disorders.

Dr. Mario Plebani

Errors in Laboratory Medicine and Patient Safety

Mario Plebani obtained his medical degree summa cum laude from the Medical School of the University of Padova in 1975. He completed residency training and specialization in Laboratory Medicine (1978), and subsequently in Gastroenterology (1983), at the same University. In 1991 he was appointed Head of the Clinical Laboratory of the University-Hospital in Padova and in 2001 Chair of the Department of Laboratory Medicine at the same University-Hospital. In 2003 he was appointed Full Professor of Clinical Chemistry and Clinical Molecular Biology (BIO/12) at the Medical School of the University of Padova, maintaining the direction of the Department of Laboratory Medicine in the same University-Hospital.

Currently, he is also Director of the Post-graduate School in Clinical Biochemistry and President of the Course for Medical Technologists at the Medical School of the Padova University. Past-President (2004-2008) of the International Society of Enzymology (ISE) and Past-President of the Italian Society of Clinical Biochemistry and Molecular Clinical Biology (SIBioC) for the years 2003 and 2006-2009. Currently he is President of the Italian Federation of Scientific Societies of Laboratory Medicine (FISMeLAB), Editor in Chief of Clinical Chemistry and Laboratory Medicine (CCLM) and Associate Editor of other accredited journals, he has published 700 original papers in accredited journals and is a recipient of some national and international Awards, including the 2008. AACC AWARD for Outstanding Clinical Laboratory Contributions to Patient Safety.

Dr Gifford Batstone

Standardisation of LIS connectivity - National Laboratory Medicine Catalogue

Dr. Gifford is a chemical pathologist at Brighton and Sussex University Hospitals where he also involved in developing the curriculum for chemical pathology and creating learning materials for medical students.

He became the National Clinical Lead for Pathology in the Clinical Directorate of DH Informatics Directorate in March 2008 and is responsible for developing IT support for the requesting and reporting cycle for pathology tests. This involves the creation of a National Laboratory Medicine Catalogue, revising the current Pathology Bounded Code List, determining the professional requirements for the content of pathology messages and working with messaging experts on the best routes for transmitting requests and reports, including the secondary uses of laboratory data by disease registries, screening programmes, disease surveillance, audit and service commissioning as well as research.

SESSION 1

Laboratory Medicine

Dr. Barry White

National Director for Clinical Strategy and Programmes,
Dr. Steevens' Hospital, Dublin

Clinical Strategy and Programmes



Errors in Laboratory Medicine and Patient Safety

Laboratory medicine has a long history of careful attention to quality assurance, standard setting and performance monitoring. This is an important foundation to build upon for reducing the risk of errors and improving patient safety. In the last decade, the approach to errors in laboratory medicine has been strongly modified, moving from a 'laboratory-centered' scenario which recognised only analytical errors, to a 'patient-centered' scenario that focus on errors in the total testing process.

Current evidence demonstrates that pre- and post-analytic steps are much more vulnerable to errors than the analytic phase. In addition, on exploring the beginning and the end of the testing loop, it emerges that currently these steps -'pre'- and 'post'-analytic steps- performed neither in the clinical laboratory nor, at least in part, under the control of laboratory personnel, are more error-prone than others. Analogously, in the last few decades, the concept of patient safety evolved and emerged to assume an increasing importance, but most available data on errors in health care focus on medication-related errors, particularly in hospitals, and related adverse events. However, in the last few years large-scale surveys demonstrated that patients and physicians perceive that diagnostic errors are common and of concern. As a matter of fact, throughout the last decade, diagnostic errors have become the most prevalent type of malpractice claim in the United States. The diagnostic process, in fact, consists of numerous clinical steps, stretched across multiple providers, and errors that could harm patients result from the alignment of multiple breakdowns, which in turn stem from a confluence of contributing factors. Errors in laboratory medicine play a relevant role in the context of diagnostic errors and call for new efforts by laboratory professionals. The path towards safety and quality in laboratory medicine has moved from the analytical phase to a patient-centered scenario in which laboratory professionals have to take care of all steps and procedures performed from test ordering to results interpretation and this should be done only through teamwork and interdisciplinary co-operation.

SESSION 1

Laboratory Medicine

Dr. Gifford Batstone

Clinical Lead for Pathology,

Clinical Division DH Informatics Directorate, NHS

Standardisation of LIS connectivity - National Laboratory Medicine Catalogue

About seven years ago pathology professionals working with the DH informatics team created a system for the reporting of biochemistry, haematology and immunology results. Expanding this approach to include microbiology, virology, histopathology, cytology and results of screening programmes proved more complex.

With the introduction of electronic requesting of diagnostic tests, the requirement for a system for both requesting and reporting and covering all pathology disciplines became apparent. Funding for this development, known as the National Laboratory Medicine Catalogue (NLMC), came from DH Pathology and Connecting for Health with the Royal College of Pathologists hosting the governance process on behalf of pathology professions.

To promote interoperability between systems and to promote the use of pathology data for secondary purposes, it was agreed that the NLMC would be in the form of a relational database based on a structure model rather than a traditional flat file. The requesting side links the request item with appropriate specimen types, patient pre-conditions, laterality, topography and morphology (when needed) and method of collection. Reporting includes analyte measured, analysed specimen type, unit of measurement (based on UCUM units), reference range/decision limit and an indicator for data combination when data comes from different sources. All items are being SNOMED-CT coded.

The NLMC is currently being incorporated into pathology requesting and reporting in three pilot sites.

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SESSION 2

Cardiology and Biochemical Markers of Heart Disease



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Chair

Chairperson: Dr. Sean Cunningham, St. Vincent's University Hospital, Dublin.

Speakers

Dr. Paul Collinson

High Sensitivity Troponin and the pain to come

Dr Paul Collinson studied at St Catharines College, Cambridge (Medicine and Biochemistry) and St Thomas Hospital, London. Despite an eclectic career path, he was appointed a Consultant currently at St George's Hospital, London. His doctoral thesis was on the early diagnosis of AMI with subsequent work on the pathogenesis, diagnosis and management of acute coronary syndromes. He has a special interest in the cost economics of cardiac care and point of care testing. Dr Collinson has performed two prospective RCT's on point of care testing and published over 200 papers and review articles, over 220 abstracts and 15 book chapters. In his spare time he likes SCUBA diving and photographing sharks - especially the ones with big teeth.

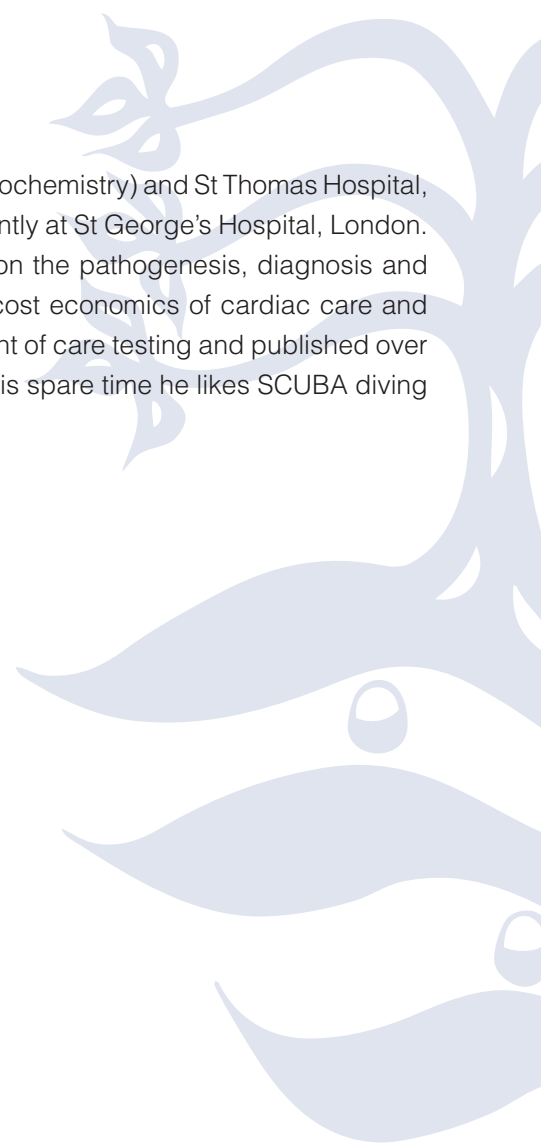
Prof. Ken McDonald

Heart Failure Unit, St. Vincent's Healthcare Group

Dr. Paul Collinson

Novel biomarkers – fact or fantasy

See biography above.



SESSION 2

Cardiology and Biochemical Markers of Heart Disease

Dr. Paul Collinson

St. George's Hospital,
London

High Sensitivity Troponin and the pain to come

Why have sensitive troponin assays been developed?

Sensitive troponin assays have been developed to meet the diagnostic goals set by the universal definition of myocardial infarction (MI). They need to be able to accurately measure a cardiac troponin value at the 99th percentile of a reference population with adequate precision. The analytical advantages of sensitive troponin assays include improved analytical imprecision at concentrations below the 99th percentile and the ability to fully define a reference distribution, instead of one where the majority of the reference population has an undetectable value. This means sensitive troponin assays define a true 99th percentile.

What is the clinical role of sensitive troponin assays in the patient with chest pain?MI

Clinically the improved sensitivity translates into the ability to diagnosis MI earlier, possibly within 3 hours from admission and the ability to use rate of change of troponin (delta troponin) for diagnosis. Very sensitive assays may, in appropriately selected populations (perhaps with the addition of delta troponin) allow diagnosis on hospital admission or within 1-2 hours of admission. Sensitive troponin assays challenge the concept of early troponin measurement being diagnostically insensitive. Sensitive troponin assays have been shown to detect troponin rises before that of other cytoplasmic markers such as myoglobin or creatine kinase MB. This questions the role of other cytoplasmic markers or marker panels which are said to allow diagnosis in the early phase of myocardial injury.

What are the disadvantages of sensitive troponin assays in the patient with chest pain?MI

A more sensitive troponin method also means an increase in the number of other clinical conditions where an elevated troponin will be reported. This is perceived as a problem. The reality is that troponin elevations in patients without acute coronary syndromes were described with the first generation troponin assays. The difference is that, as assay sensitivity has improved, a broader range of clinical conditions with troponin elevations has been documented. An elevated troponin occurring in patients without suspected acute coronary syndromes (ACS) has, in all studies to date where outcome has been examined, been shown to indicate an adverse prognosis whatever the underlying clinical diagnosis. Troponin elevation therefore represents a diagnostic opportunity. Failure of elevation means a good prognosis allowing early, safe hospital discharge whilst a raised value requires investigation and should help prevent clinically significant pathology being overlooked. Stable troponin elevation in a range of clinical conditions such as renal failure or heart failure challenges the current paradigms of the pathophysiology of these diseases. Troponin elevation is a specific biomarker of ongoing myocardial injury in a range of clinical conditions so can, potentially, act as a monitoring tool for the effects of interventions. Troponin elevations in apparently healthy populations may also indicate those at high risk where preventive strategies will be most effective.

What are the challenges to implantation in routine clinical practice.

Sensitive troponins do present a challenge to the laboratory and the clinician. For the laboratory, the diagnosis of MI requires a change in troponin value. One of the ongoing debates is to define what constitutes an appropriate value for delta troponin. For the clinician, the challenge is to shift from a simplistic yes/no diagnosis of MI based on a single troponin value to a diagnosis that utilises early troponin changes as part of the clinical picture and to relate the new class of detectable troponin elevation in patients with ischaemic myocardial disease to existing clinical guidelines and trial evidence.



SESSION 2

Cardiology and Biochemical
Markers of Heart Disease

Prof. Ken McDonald

Heart Failure Unit,
St. Vincent's Healthcare Group

Heart Failure – Diagnosis and Management



SESSION 2

Cardiology and Biochemical Markers of Heart Disease

Dr. Paul Collinson

St. George's Hospital,
London

Novel biomarkers – fact or fantasy

The measurement of the cardiac troponins, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are the gold standard biochemical tests that define myocardial infarction (MI). It is an attractive hypothesis that addition of a second marker, measured on admission, will further improve diagnostic efficiency. Other markers might also add further refinement to risk stratification.

The other markers which might be used can be broadly categorised into three groups. The first are markers of plaque destabilisation. These may be inflammatory markers such as C reactive protein or interleukin 6 or more direct markers of plaque instability such as myeloperoxidase or pregnancy associated plasma protein. The second group are markers of myocardial injury. This may be a direct marker of myocardial injury or ischaemia such as heart type fatty acid binding protein or a marker of myocardial stress and remodelling such as B type natriuretic peptide, growth differentiation factor 15 or ST2/interleukin 33. The final group comprises markers of vascular stress such as copeptin or adrenomedullin. There are published studies showing that all of these markers can be added to troponin measurement with apparently improved diagnostic or prognostic accuracy. However, few of these studies have used a contemporary high sensitivity assay and all suffer from the problem of poor specificity. They may be useful as rule out markers but the significance of a positive result and its impact on management remains to be defined.



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- Cytogenetics
- Cytology
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SESSION 3

Cystic Fibrosis



Chair

Chairperson: Ms. Deirdre Deverell, Children's University Hospital, Temple St., Dublin.

Speakers

Prof. Charles Gallagher

Cystic Fibrosis - an Evolving Disease of Middle Age and the Elderly

Professor Charles Gallagher is Consultant Respiratory Physician at St. Vincent's University Hospital and University College Dublin. He trained in Dublin and Canada. He was Professor of Medicine and Head of the Department of Respiratory Medicine at the University of Saskatchewan in Canada before taking up his current post in 1997. He has published over 80 peer reviewed scientific articles.

Prof. Philip D. Mayne

Screening For and Diagnosis of Cystic Fibrosis

Professor Philip Mayne MD, BA (Mod), MSc, FRCPI, FRCPath, FFPPath (RCPI) is director of the National Newborn Bloodspot Screening Laboratory and consultant paediatric chemical pathologist at the Children's University Hospital, Temple Street, Our Lady's Children's Hospital, Crumlin and the Rotunda Hospital. He is an associate professor in biochemistry (MCT) and in paediatrics at the Royal College of Surgeons in Ireland.

Philip Mayne graduated from Trinity College, Dublin in biochemistry and medicine. He spent a number of years in clinical medicine before moving to London to train in chemical pathology. He held a number of consultant appointments including one at the Westminster and Westminster Children's Hospitals before returning to Dublin.

Dr. Edward McKone

The Genetics of Cystic Fibrosis

Dr Edward McKone is a Consultant Respiratory Physician in the National Referral Center for Adult Cystic Fibrosis, St. Vincent's University Hospital. A graduate of Trinity College Dublin, he completed his initial respiratory training including MD thesis in St. Vincent's University Hospital. He subsequently entered a three year fellowship in Pulmonary and Critical Care Medicine at the University of Washington, Seattle followed by four years on faculty as a consultant physician in Pulmonary and Critical Care Medicine. In 2006, he was appointed to St. Vincent's University Hospital, Dublin where he is currently a respiratory physician with clinical and research interests in the areas of cystic fibrosis, clinical genetics, epidemiology and bronchiectasis.

SESSION 3

Cystic Fibrosis

Prof. Charles Gallagher

National Referral Centre for Adult Cystic Fibrosis,
St. Vincent's University Hospital, Dublin

Cystic Fibrosis - an Evolving Disease of Middle Age and the Elderly

Cystic Fibrosis is the most common inherited life-threatening disease in Ireland. It is inherited as an autosomal recessive condition. Therefore if two carriers of a CF gene have a child together, there is a 1 in 4 chance that the child will have Cystic Fibrosis. Ireland has the highest incidence of Cystic Fibrosis carriers and therefore of Cystic fibrosis in the world. Approximately 1 in 19 Irish people are carriers of the CF gene and therefore the incidence of Cystic fibrosis is approximately one in 1450 births. There are now over 1100 people with Cystic Fibrosis in Ireland

CF is a disease of abnormal ion, especially chloride and sodium, transport that is caused by mutations in the CF gene. CF affects, or can affect, almost all organs. However the organs most involved are the lungs, sinuses, the pancreas, the gastrointestinal tract, the reproductive system and the skin. The major clinical problems usually include recurrent chest infections and bronchiectasis, sinusitis, malnutrition, diabetes mellitus and liver disease. However no 2 patients are the same and nature of CF varies a lot between patients, even among siblings with CF. The differences are partly related to differences in types of CF mutations but are also related to modifier genes, environmental factors, and gender- women with CF have, on average, more severe disease than men.

The outlook for people with CF has changed a lot in recent years. 30 years ago most people with CF died in their teens or early twenties and there were few adults with CF. Nowadays the vast majority of people with CF reach adult life and there are many people with CF in their 30s, 40s, and beyond. There are people with CF in every walk of life and in almost every occupation. The improvement in prognosis is due to aggressive treatment of acute exacerbations of CF, improved nutritional treatment, new drugs and the development of dedicated Cystic Fibrosis multidisciplinary teams.

Eventually we want to see pensioners with CF and that day will come.



SESSION 3

Cystic Fibrosis

Prof. Philip Mayne

Children's University Hospital, Temple Street,
Our Lady's Children's Hospital, Crumlin
and the Rotunda Hospital

Screening For and Diagnosis of Cystic Fibrosis

The Irish National Newborn Bloodspot Screening Programme was established in 1966 to offer screening for phenylketonuria (PKU) to all newborns between days 3 to 5 of life. Since then a number of other conditions, which fulfilled in part or in full the Wilson and Jungner criteria, have been added to the programme; some have been discontinued.

Ireland has one of the highest incidences of Cystic Fibrosis in the world at approximately 1 in 1,370. Newborn screening for Cystic Fibrosis fulfils most of the Wilson and Jungner criteria and the benefits of early detection and management have been well documented in the literature.

Following approval by the Department of Health and Children, the reorganization of the paediatric Cystic Fibrosis services and changes to aspects of the existing programme, newborn screening for Cystic Fibrosis started in July 2011. A two tier immunoreactive trypsinogen (IRT)/expanded CFTR DNA mutational analysis screening approach was incorporated into the existing newborn bloodspot screening programme.

The presentation will discuss the rationale for adopting this approach and explain how the delivery of the service had to be adapted to accommodate legislation and how the potential harm associated with such a screening programme was, and could be, addressed.

SESSION 3

Cystic Fibrosis

Dr. Edward McKone

St. Vincent's University Hospital,
Dublin

The Genetics of Cystic Fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive genetic disease primarily affecting the respiratory system in Ireland.

It is caused by mutations in the CFTR gene, a large 250kbp gene located on the long arm of Chromosome 7. To date, over 1800 disease-causing mutations in the CFTR gene have been identified.

The discovery of the CFTR gene in 1989 has lead to huge breakthroughs in our understanding of CF. This talk will focus on how CF genetics have influenced how we diagnose and manage patients with CF.

We will also discuss some novel pharmacogenetic approaches to correct CFTR dysfunction which could be of major significance to Irish CF patients.

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SESSION 4

Liver Disease



Sponsored by BD Diagnostics - Preamerical Systems

Chair

Chairperson: Dr. Damian Griffin, University College Hospital, Galway

Speakers

Dr. John N Plevris

Aspects of Liver Disease; Fatty Liver and Liver fibrosis

Dr John N Plevris is a Consultant and Reader in Gastroenterology and Hepatology at The Royal Infirmary, University of Edinburgh. He graduated from the University of Athens and completed his training in Edinburgh and Amsterdam. He completed a PhD at the University of Edinburgh and he is also a Doctor of Medicine at the University of Athens. His main clinical interests include therapeutic endoscopy, general Gastroenterology and Hepatology; his research interest areas include liver failure, fatty liver, and basic science research in hepatocyte biology and liver support systems. He is an author or co-author of over 100 peer review articles and book chapters.

Prof. Munir Pirmohamed

Drug Induced Liver Injury

Munir Pirmohamed qualified in Medicine in 1985, and obtained a PhD in Pharmacology in 1993. He was awarded a Personal Chair in Clinical Pharmacology at The University of Liverpool in 2001, and in 2007, was appointed to the NHS Chair of Pharmacogenetics. He is also Head of Department of Molecular and Clinical Pharmacology and Director of the Wolfson Centre for Personalised Medicine. Professor Pirmohamed is a Member of the Commission on Human Medicines and Chair of its Pharmacovigilance Expert Advisory Group. His main area of research is in pharmacogenetics and drug safety, where he has published over 250 articles.

Prof. Aiden McCormick

Liver Transplantation

Prof. McCormick graduated UCD Medicine in 1979. He trained in Ireland and Canada and was a lecturer in the Royal Free Hospital School of Medicine, University of London from 1988 to 1994. He has been a Consultant Hepatologist in St Vincent's University Hospital and the National Liver Transplant Programme since 1994. He was appointed Newman Clinical Research Professor in UCD 2002.

SESSION 4

Liver Disease

Dr. John N Plevris

The Royal Infirmary of Edinburgh

Aspects of Liver Disease; Fatty Liver and Liver fibrosis

Traditionally, the main cause of Fatty Liver has been alcohol abuse. Non-Alcoholic Fatty Liver Disease (NAFLD), however, is becoming increasingly common in the western world as a consequence of obesity. In USA alone, up to 30% of the population are overweight or obese.

In the majority of patients with NAFLD, metabolic syndrome is present and a significant percentage of these patients also suffer from diabetes (mainly type II). Patients with NAFLD can progress to Non-alcoholic steatohepatitis (NASH) and eventually to liver cirrhosis. Once cirrhosis develops such patients are at increased risk of hepatocellular carcinoma. End-stage liver disease due to NAFLD is now the premier indication for liver transplantation in many western world transplant centres.

The exact pathophysiological mechanisms that lead to liver inflammation and fibrosis are not completely understood. Central role to these events play the development of insulin resistance (both peripheral and hepatic), the production of inflammatory mediators from adipose tissue and the increased levels of oxygen reactive species, which induce hepatic mitochondrial dysfunction and promote the formation of fat droplets within the hepatocyte. The order of events is still debated. High fat in combination high carbohydrate diet can induce the above biochemical abnormalities.

Fibrosis is the result of activation of stellate cells within the liver, in combination with the reduced ability of liver macrophages to break down collagen. Any repetitive (chronic) insult to the liver, would not only lead to hepatic mass reduction, but also to development of fibrous tissue starting from the liver sinusoids. This eventually leads to deranged liver architecture (nodule formation).

The only reliable method of diagnosing the presence of liver fibrosis until recently has been a liver biopsy. Liver biopsy is invasive and associated with some morbidity or even mortality. Over the last few years a number of non-invasive tests of fibrosis have been developed with acceptable sensitivity and specificity. These include estimation of serum hyaluronic acid levels, measurement of a combination of more than one biochemical markers (Fibrotest) and techniques that measure liver stiffness by transient elastography (Fibroscan®). Such methods are now widely applied and have reduced the routine usage of liver biopsy to cases that diagnostic dilemmas exist.

SESSION 4

Liver Disease

Prof. Munir Pirmohamed

NHS Chair of Pharmacogenetics

Department of Molecular and Clinical Pharmacology,
The University of Liverpool

Drug Induced Liver Injury

Drug-induced liver injury is an important public health problem, being caused by over 1000 drugs. It is one of the commonest reasons why drugs are withdrawn from the market. Although there are some dose-dependent hepatotoxins, such as paracetamol, most drugs do not show a clear dose response relationship, where the toxicity is sometimes termed idiosyncratic.

Drugs can cause many different forms of liver injury, but I will be concentrating on the acute forms characterised by either hepatocellular necrosis, hepatitis or cholestasis. An important area for further investigation in liver injury is the identification of biomarkers which will add value, or be superior, to the current measurement of transaminases. There is a great deal of interest in this area, with the focus being on novel protein biomarkers as well as on micro-RNA species. Allied to this is a requirement to improve our understanding of the mechanism(s) of liver injury.

Even with paracetamol, we do not fully understand how the reactive metabolite from paracetamol causes hepatocyte damage. Thus further research in this area is important in its own right, but will also provide insights into the mechanisms of idiosyncratic liver injury. Clearly with the dose-dependent hepatic toxins such as paracetamol, anybody who takes a large enough dose will get liver injury, although there is some variability in susceptibility even with paracetamol. With idiosyncratic toxins, we cannot currently predict with any great certainty as to who will develop the liver injury. The availability of genomic information and high throughput genomic technologies is now allowing us to be able to unravel genetic factors predisposing to drug-induced liver injury. In particular, recent research has uncovered very strong associations with the HLA genes and liver injury caused by many drugs, including flucloxacillin, co-amoxiclav and lumiracoxib. Many of these issues will be covered in the presentation.

SESSION 4

Liver Disease

Prof. Aiden McCormick
St Vincent's University Hospital,
Dublin

Liver Transplantation



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POSTER PRESENTATIONS



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Poster Index

- 1 Bone Health in a Cohort of Irish Duchenne Muscular Dystrophy (DMD) Patients**
N Mc Sweeney¹, M.J. Mc Kenna^{2, 3}, C. Mc Donnell⁴, N. Murphy⁴, D. Webb⁵, S. van der Kamp², M. Kilbane³, M. O'Keane³, B.Lynch^{1, 6}.
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⁵ Department of Paediatric Neurology, The Children's University Hospital⁶, Dublin, Ireland*
- 2 Vitamin D Status in Ireland: Interpretation Post IOM**
M. J. McKenna, B. F. Murray, M. Kilbane
Metabolism Laboratory, St. Vincent's University Hospital
- 3 Lipid profile and bone health in free living elderly men and women**
By E Laird¹, M Ward¹, H McNulty¹, M Healy², MC Casey², JJ Strain¹ and JMW Wallace¹,
*¹Northern Ireland Centre for Food and Health (NICHE) University of Ulster Coleraine BT52 1SA ,
² The Mercers Institute for Research on Ageing (MIRA) and the Department of Biochemistry, St James's Hospital, Dublin, Ireland*
- 4 A look back at GP requesting of vitamin D over a 12-month period in St. James's Hospital**
Healy M, Cox G, Gannon P, Crowley V
Biochemistry Department, St. James's Hospital, Dublin 8
- 5 Evaluation of a liquid chromatography tandem mass spectrometry (LC-MS/MS) method for the determination of Cyclosporine and Tacrolimus**
Feely A, Crowley V, Cox G, Healy M
Biochemistry Department, St. James's Hospital, Dublin 8
- 6 The number of total PSA tests continues to rise; a survey of laboratory services in Ireland 2008-2010; A laboratory survey**
Frances J Drummond, Harry Comber, Linda sharp
National Cancer Registry, Ireland
- 7 An Evaluation of NT-proBNP Testing in the Diagnosis of Heart Failure**
Hamilton JS, ¹Sharma D, Smye M, ¹Nicholls DP, Auld PW.
*Department of Clinical Biochemistry, Royal Victoria Hospital, Belfast.
¹Department of Cardiology, Royal Victoria hospital, Belfast*

Poster Index

- 8 Association between Serum Vitamin D levels and Severity of Asthma in an Irish Population**
K. Hutchinson^a, K. Bolger^b, L.J. Cormican^b, C. M. Burke^b, C. Kerley^b, J.L. Faul^b
*^aDepartment of Clinical Chemistry, Biomnis Ireland, Dublin,
^bAsthma Research Centre, Connolly Hospital, Dublin, Ireland.*
- 9 ETHYL GLUCURONIDE: A marker for alcohol use in methadone maintenance patients**
Louise Lawlor, Siobhan Stokes, Grainne Smith
The Drug Treatment Centre Board Laboratory, Dublin.
- 10 Pyridoxine and Pyridoxal Phosphate Responsive Neonatal Seizure**
Borovickova I¹, Deverell D¹, Lynch B², Mayne PD¹
*¹Department of Clinical Biochemistry, Children's University Hospital, Temple Street, Dublin 1
²Neurology Department, Children's University Hospital, Temple Street, Dublin 1*
- 11 Fumarate Hydratase Deficiency – Irish Cases and Future Implications for Identification of Carrier Status of this Disorder.**
Borovickova I¹, Fitzsimons PE¹, Hughes J², Monavari AA², and Mayne PD¹.
*¹Department of Clinical Biochemistry, Children's University Hospital, Temple Street, Dublin.
²National Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple Street, Dublin 1.*
- 12 Glycogen Synthetase Deficiency: A rare cause of ketotic hypoglycaemia**
Fitzsimons PE¹, Borovickova I¹, Kozdoba O², Knerr I², Crushell E², and Mayne PD¹
*¹ Department of Clinical Biochemistry, Children's University Hospital, Temple Street, Dublin 1,
² National Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple Street, Dublin 1.*
- 13 Seroepidemiology of the Recent Mumps Virus Outbreaks in Ireland**
J. Hassan, J. Dean, E. Moss, M. Carr, W. Hall & J. Connell
*National Virus Reference Laboratory & Centre for Research In Infectious Diseases,
School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4.*



Poster Index

14 Epstein-Barr Virus Gene Expression, Human Leukocyte Antigen Alleles and Viral Loads in Paediatric Renal Transplant Patients.

J. Moran,^{1,2} M. Carr,^{1,2} A. Waters,^{1,2} J. Connell,¹ A. Awan,³ W. Hall^{1,2} & J. Hassan^{1,2}

¹ National Virus Reference Laboratory, ² Centre for Research in Infectious Diseases, School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4 & ³ Department of Nephrology, Children's University Hospital, Temple Street, Dublin 1.

15 Is the Measurement Epstein Barr Virus Early Antigen IgG of Diagnostic Value?

Andrea Crowley^a, Jeff Connella, Kirsten Schaffer^b, William Hall^a & Jaythoon Hassana

^a National Virus Reference Laboratory, University College Dublin, &

^b National Liver Transplant Unit, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

16 An Audit of the Number & Frequency of Unacceptable Specimens & Review of Reasons for Rejection within the Biochemistry Laboratory

S Kelly, C Hatton, S Cunningham, B Larkin, D Murphy

Department of Biochemistry, St Vincent's University Hospital, Elm Park, Dublin 4

17 Neutrophil function assessed by Pholasin® based bioluminescence assay. Results of a pilot study.

John Williams¹, Jan Knight², Brian Moore³ and Andy Hodgson¹.

¹ Pathology Department, Sligo General Hospital, ² Knight Scientific Limited, Playmonth, UK.

³ Independent Consultant Physiologist

18 Profound High Bone Turnover in X-Linked Hypophosphataemic Rickets with very "Hungry Bones" following Total Parathyroidectomy

O'Keane M, Kilbane M, Crowley R, McKenna MJ, Cunningham SK

Metabolism Laboratory and Department of Endocrinology, Clinical chemistry Group of laboratories, St. Vincent's University Hospital, Dublin 4.

Poster Index

19 Evaluation of Elecsys Troponin T hs (High Sensitive) Assay versus Troponin T 4th Generation Assay on the Roche Modular Analytics E170

Eileen Byrne, Alison Breslin, Rowland J Reece, Sean K Cunningham

Clinical Biochemistry Department, St Vincent's University Hospital, Dublin 4

20 Enzymatic creatinine assay is preferable to Jaffe assay for monitoring renal function in patients being treated with Cefoxitin

L Kavanagh-Wright¹, R Reece¹, M Moran², C Gallagher³ and OC Maguire¹

¹Clinical Biochemistry Department, ²Pharmacy Department, ³Department of Respiratory Medicine, St. Vincent's University Hospital, Elm Park, Dublin 4



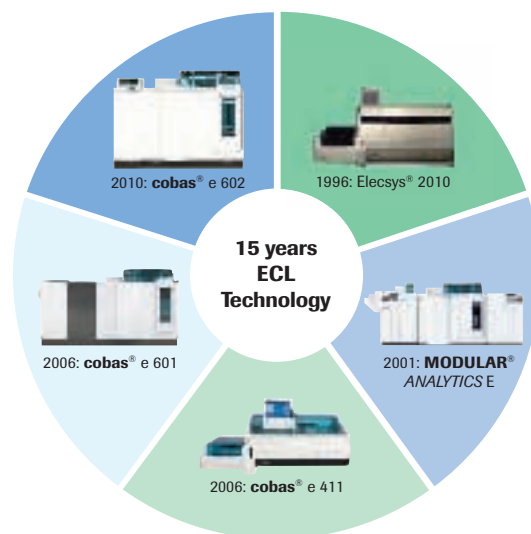
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Poster 1

Bone Health in a Cohort of Irish Duchenne Muscular Dystrophy (DMD) Patients

N Mc Sweeney¹, M.J. Mc Kenna^{2, 3}, C. Mc Donnell⁴, N. Murphy⁴, D. Webb⁵, S. van der Kamp², M. Kilbane³, M. O'Keane³, B.Lynch^{1, 6}

Introduction:

Department of Paediatric Neurology, The Central Remedial Clinic¹, DXA Unit² and Metabolism Laboratory³, St. Vincent's University Hospital, Department of Endocrinology, The Children's University Hospital⁴, Department of Paediatric Neurology, Our Lady's Children's Hospital,⁵ Department of Paediatric Neurology, The Children's University Hospital⁶, Dublin, Ireland

Objectives:

We sought to determine the prevalence of low bone mineral density (BMD) and vitamin D deficiency, and the response to supplementation in DMD.

Methods:

We measured BMD Z-score at the whole body and spine, serum 25-hydroxyvitamin D (S-25-OHD), serum procollagen type I aminopropeptide (S-PINP) and urine aminoterminal crosslinked telopeptide of type 1 collagen (Ur-NTx). Following supplementation with vitamin D (400-800 IU/d) and calcium (500-1000 mg/d), S-25-OHD was repeated. Results are expressed as mean±SD.

Results:

Forty-seven patients were studied aged 11.4±4.3 years; 53% were ambulant; 55% were on glucocorticoids; 21% had a fracture history. BMD was measured in 39 (spine only = 6; whole body only = 4; both = 29) with Z-score <-2.0 in 32% at spine and in 42% at whole body. Non-ambulant compared to ambulant had lower Z-score at spine (P=0.029) and whole body (P=0.004), but were not different with respect to either fracture history or steroid therapy. Spine Z-score correlated with age (r=-0.527; P<0.001), ambulant status (rho=0.383; P=0.025) and whole body Z-score (r=0.452; P=0.016). Whole body Z-score did not correlate with age or ambulant status. In multiple regression models, age was the sole determinant of spine Z-score (r²=0.32; P=0.001) and ambulant status was the sole determinant of whole body Z-score (r²=0.20; P=0.017). S-25-OHD was below 30 nmol/L in 38% at baseline and in 5% after supplementation. At baseline, S-PINP was low in 33%, but Ur-NTx was elevated in 100%.

Conclusion:

Low BMD, vitamin D deficiency, low bone formation and high bone resorption are common in DMD.



Poster 2

Vitamin D Status in Ireland: Interpretation Post IOM

M. J. McKenna, B. F. Murray, M. Kilbane, Metabolism Laboratory, St. Vincent's University Hospital

Background:

The Institute of Medicine (IOM) in a recent public health report on dietary requirements for calcium and vitamin D in North America contained three important findings for clinicians: (1) serum 25-hydroxyvitamin D (S-25OHD) levels above 50 nmol/L meet the needs of 97.5% of the population for all life stages, (2) S-25OHD levels above 125 nmol/L could indicate those at risk of harm from over-replacement, and (3) a simulated dose-response formula is given for estimating the expected S-25OHD based on total oral vitamin D intake. We and others over the past 30 years have identified high prevalence of poor vitamin D status in Ireland. So we reviewed our recent experience of vitamin D status in the light of the IOM report both in healthy subjects and those with illnesses.

Methods:

S-25OHD was measured in a diverse group of Irish subjects (n=1254): healthy adults during winter, patients with multiple sclerosis during winter; mothers at term and cord samples from their offspring; preterm infants at about 3 weeks old and again at about 15 weeks old; osteoporosis patients on low-dose vitamin D supplementation; cystic fibrosis patients on low-dose vitamin D supplementation.

Results:

In healthy adults during winter 33% are ≥ 50 nmol/L compared to 28% of MS patients. At term birth only 13% of infants are ≥ 50 nmol/L, similar to preterm infants at 3 weeks. After prolonged oral intake of 400 IU/d 86% of preterm infants were ≥ 50 nmol/L, but 25 % were >100 nmol/L and 8% were >125 nmol/L. Osteoporosis patients on supplementation (723 ± 200 IU/d) achieved this level in 91% but cystic fibrosis patients on supplementation (1380 ± 447 IU/d) were less successful (Table 1). In a previous study we recalculated the response to low-dose vitamin D and noted an increase 8.4 nmol/L/100 IU that is fourfold higher than the oft quoted expected rise of 1.8 nmol/L/100 IU, but was similar to the IOM simulated dose-response formula.

Conclusion:

The IOM offers a standard and a gauge for guaranteeing adequate vitamin D status to the Irish population but in our more northerly latitude we have an even greater dependence on oral intake in ensuring optimal vitamin D status. We find a high prevalence of poor vitamin D status in our unsupplemented groups, but for many infants 400 IU/d is excessive.

Table 1

Groups	N	S-25-OHD nmol/L				
		<30	30-49	≥ 50	>100	>125
Healthy adults during winter	229	21%	46%	33%	0%	0%
Multiple sclerosis patient during winter	331	40%	32%	28%	2%	1%
Healthy pregnant women at term	39	21%	34%	45%	3%	0%
Umbilical cord samples at term	39	59%	28%	13%	0%	0%
Preterm infants at 3 weeks	272	21%	65%	14%	1%	0%
Preterm infants at 15 weeks (supplemented)	148	3%	11%	86%	25%	8%
Osteoporosis outpatients (supplemented)	91	1%	8%	91%	20%	2%
Cystic fibrosis patients (supplemented)	105	23%	28%	49%	8%	3%



Poster 3

Lipid profile and bone health in free living elderly men and women

**By E Laird¹, M Ward¹, H McNulty¹, M Healy², MC Casey², JJ Strain¹ and JMW Wallace¹,
¹Northern Ireland Centre for Food and Health (NICHE) University of Ulster Coleraine BT52 1SA,
²The Mercers Institute for Research on Ageing (MIRA) and the Department of Biochemistry,
St James's Hospital, Dublin, Ireland.**

Introduction:

Osteoporosis and osteopenia are increasingly common conditions associated with decreased bone mineral density (BMD) and increased bone fragility. Osteoporosis is linked with atherosclerosis and specific lipid profiles have been associated with BMD^{1,2}. The aim of this study was to assess the relationship between lipid profile and bone health in a sample (n=1000) of participants from the Northern Ireland cohort of the TUDA (Trinity Ulster Department of Agriculture) study. Participants were recruited based on the following criteria; aged >60 years, hypertension (>140/90mm/Hg) born (or have parents born) on the Island of Ireland and no evidence of severe dementia. A lipid profile was measured and BMD of the total hip, femoral neck and lumbar vertebrae were measured using total body dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Healthcare, UK). Individuals were classified as normal, osteopenic and osteoporotic using BMD T-scores³ and also according to established cut-offs for high density lipoprotein (HDL) and low density lipoprotein (LDL) concentration⁴.

There were no significant associations between total cholesterol or LDL concentrations and BMD at any site. However, individuals in the osteoporotic group had significantly higher concentrations of HDL than those in the osteopenic (<0.01) or normal (<0.01) group. Sex specific analysis showed that men with the higher concentrations of HDL had significantly lower femoral neck and vertebral T-score (<0.001); these differences were not apparent in women. We speculate that HDL may negatively impact on bone health possibly via decreasing the osteogenic differentiation of mesenchymal stem cells (MSCs) to osteoblasts as suggested previously¹.

We would like to acknowledge the co-funding for this research from the Irish Department of Agriculture and the Northern Ireland Department for Employment and Learning through its "Strengthening the all-Island Research Base" initiative.

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Poster 4

A look back at GP requesting of vitamin D over a 12-month period in St. James's Hospital

Healy M, Cox G, Gannon P, Crowley V
Biochemistry Department, St. James's Hospital, Dublin 8

Introduction:

Vitamin D is a nutrient which has recently received considerable attention. It has been implicated in the pathogenesis of numerous diseases e.g. osteoporosis, various forms of cancer, cardiovascular disease, diabetes and multiple sclerosis. With this awareness has come an exponential increase in the number of requests for its analysis.

One aspect of this has been an increase in GP requests for the test. To examine this more closely we undertook a review of such requests made over a 12-month period (August 2010 – July 2011).

25-hydroxyvitamin D (25OHD), the marker for vitamin D status, was analysed by mass spectrometry (AB SCIEX API 4000). The thresholds for 25OHD used in St. James's Hospital are <25 nmol/l-deficient; 25-75 nmol/l-insufficient; >75 nmol/l-optimal. Values > 350 nmol/l are considered toxic.

1386 requests were made over the year. Female to male ratio was 3:1. The number of requests ranged from 1 to 327 for individual GPs. Overall, the results indicate a significant degree of deficiency/insufficiency with 61% of patients having sub-optimal 25OHD concentrations. 123 females (9%) and 62 males (5%) had concentrations <25 nmol/l. 849 females (61%) and 217 males (16%) were in the insufficient range.

Looking at age-ranges there was no statistical difference between males and females at age ≤ 20 or 81-100 years. Females showed an average difference of + 9.0 nmol/l compared to males in age ranges 21-40, 41-60 and 61-80.

Many of the clinical details supplied did not refer to specific factors for requesting vitamin D. A substantial number were non-specific, e.g. fatigue, weight loss, check-up. 90 patients (7%) had repeat measurements with intervals ranging from 2 weeks to 11 months. In 68% of these 25OHD remained insufficient.

The lack of agreed guidelines is a concern in determining the efficacy of requesting a vitamin D. Apart from a set of specified criteria "routine" requesting of vitamin D is not indicated. However, to address endemic hypovitaminosis, a "don't test, just treat" approach has been suggested.

Poster 5

Evaluation of a liquid chromatography tandem mass spectrometry (LC-MS/MS) method for the determination of Cyclosporine and Tacrolimus

Feely A, Crowley V, Cox G, Healy M

Biochemistry Department, St. James's Hospital, Dublin 8

Introduction:

The calcineurin inhibitors cyclosporine and tacrolimus are critical components of most immunosuppression protocols. The narrow therapeutic indices of these drugs require close monitoring of blood concentrations to prevent rejection and minimise toxicity. Traditionally therapeutic monitoring of these drugs has relied on immunoassay. However, the antibodies in these assays cross-react with metabolites of the drugs. This lack of specificity influences estimation of the therapeutic range of these compounds often leading to overestimation of drug concentrations. More recently LC-MS/MS methods have been developed which allow the drugs to be assayed both simultaneously and independently of their metabolites.

This project was initiated to validate a commercial kit method for quantification of cyclosporine and tacrolimus by mass spectrometry (Chromsystems GmbH, Munich). The kit contains solvents, columns, calibrators, controls and internal standards. Samples are extracted initially by protein crash and online using solid phase extraction. The instrumentation consisted of a Shimadzu Ultra Fast Liquid Chromatograph linked to an AB SCIEX API 4000 mass spectrometer using electrospray ionisation run in positive mode.

Several parameters were assessed during the validation; imprecision, linearity, accuracy, stability, carryover and method comparison.

Total imprecision for cyclosporine and tacrolimus varied from 2.6-7.2% and 3.1-11.7% respectively for a range of concentrations. The method was linear to 50.1 µg/l for tacrolimus and 2150 µg/l for cyclosporine. Accuracy deviated by < 5% from 6 external QA samples with known concentrations. 7 day storage at 4°C resulted in a reduction in concentration of 2.4% for tacrolimus and 8.8% for cyclosporine. Carryover was zero for tacrolimus and 0.11-0.21% for cyclosporine. Samples previously assayed by immunoassay (Abbott Architect i2000) were reanalysed by mass spectrometry. LC-MS/MS showed a negative bias compared to immunoassay with a mean difference of -1.02 µg/l for tacrolimus and -6.6 µg/l for cyclosporine.

Advantages of mass spectrometry over immunoassay: (1) Measures immunosuppressants simultaneously (2) Specificity (3) Cost savings compared to immunoassay.



Poster 6

The number of total PSA tests continues to rise; a survey of laboratory services in Ireland 2008-2010; A laboratory survey

Frances J Drummond, Harry Comber, Linda sharp
National Cancer Registry, Ireland.

Introduction:

Prostate cancer incidence in Ireland is the highest in Europe. PSA testing has contributed to this trend. The aim of this study was to investigate the trends and costs of PSA testing, 2008-2010.

Methods:

A survey was developed and sent to 44 laboratories nationwide. Average costs of tPSA testing kits, consumables, labour costs, overheads and quality assurance costs were calculated from available data. Annual percentage change in number of total PSA (tPSA) and free PSA (fPSA) tests was estimated using Joinpoint.

Results:

Responses were received from 38 laboratories (response rate 86.4%). All of the non-responding laboratories measure tPSA routinely. tPSA is measured in 37 laboratories nationally. Six of the responding laboratories changed the assays used to measure tPSA, 2007-2010. The number of tPSA tests measured in the responding laboratories increased by 9.2% (95%CI 2.8;16.1%) annually, 2006 to 2010, with the majority of tPSA requests originating in general practice. During the same period the number of laboratories measuring fPSA decreased and the number of fPSA tests measured decreased by -31.8% (95%CI -36.1;-27.1) annually. Twelve of these laboratories use age-specific normal PSA values, 19 use tPSA values of 0-4ng/ml as their normal range. The total cost of a tPSA test was estimated as being between €6.32 and 7.16 depending on the kit used and the grade of staff employed.

Discussion:

The upward trend in the number of tPSA tests measured continues while the number of fPSA tests being performed has decreased steadily. Inter-laboratory variation in PSA testing practice remains an issue.

Poster 7

An Evaluation of NT-proBNP Testing in the Diagnosis of Heart Failure

Hamilton JS, ¹Sharma D, Smye M, ¹Nicholls DP, Auld PW.

Department of Clinical Biochemistry, Royal Victoria Hospital, Belfast.

¹Department of Cardiology, Royal Victoria hospital, Belfast.

Introduction:

Increasing prevalence of heart failure has increased demand on Echocardiography services, affecting waiting times and expenditure. Low levels of NTproBNP make heart failure unlikely, high levels indicate a poor prognosis.

Aims:

To evaluate use of NTpro-BNP in decision-making in diagnosis and management of heart failure, impact on Echocardiography services, and cost-effectiveness.

Methods:

Data was collected on patients with NTpro-BNP measured in May 2009. Data included age, sex, symptoms, co-morbidities, ECG, reason for request, NTpro-BNP result. Medical notes were examined for clinical impact of result and details of echo request.

Results:

676 requests were received. Of these, medical records of 156 patients were examined. 87 patients were male, 69 were female, mean age 69.7years. The majority presented with dyspnoea. Abnormal values enabled clinicians to initiate heart failure therapy. Raised NTproBNP in known heart failure patients led to up-titration of therapy. Normal NTpro-BNP excluded heart failure as cause of symptoms in 44 patients. Of these 44 patients, 25 had no Echo and were therefore appropriately screened. However, 17 patients had Echo despite normal NTpro-BNP and were thus inappropriately investigated. NTpro-BNP analysis costs £12, Echo costs £75. Total cost - 156 tests @ £12 = £1872. Cost saving for 25 patients appropriately screened and not referred for Echo - $25 \times £75 = £1875$. 17 patients were screened inappropriately costing $(17 \times £75) + (17 \times £12) = £1479$. If these patients were appropriately screened £1275 would have been saved and waiting lists reduced.

Conclusions:

This audit shows NTpro-BNP testing is useful when requested appropriately. NTproBNP expedites the patient journey ensuring correct clinical referral and avoidance of inappropriate investigation.





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Poster 8

Association between Serum Vitamin D levels and Severity of Asthma in an Irish Population

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Introduction: Diet and a lack of sun exposure are known to be the cause of vitamin D insufficiency in Ireland. The prevalence and severity of Asthma has been linked to an increase in the amount of time spent indoors.

The aim of this study was to measure serum vitamin D levels in 50 consecutive Irish patients (both asthmatic and non-asthmatic) with respiratory symptoms of more than 4 weeks' duration and to assess possible association with obesity and severity of Asthma.

Patient BMI (body mass index), serum total IgE, high sensitive CRP, 25- hydroxyvitamin D (25(OH)D) levels and serum eosinophil cationic protein (ECP) were measured.

Total 25(OH)D was analysed using the DiaSorin LIAISON. Serum total IgE and hsCRP were measured on the Abbott Architect ci8200 analyser. ECP was tested by ImmunoCAP Technology using fluorescent enzyme immunoassays on the IDM Phadia 250. Additionally, to evaluate the severity of asthma; bronchoscopy and spirometry were performed to ascertain the Forced Expiratory Volume (FEV₁).

Within the subject group; the prevalence of vitamin D deficiency (<25 nmol/L) was 18% in males and 43% in females. For patients <30 years old, 50% were vitamin D deficient. Significantly, patients with airway obstruction (FEV₁ less than 80% predicted), all had vitamin D insufficiency (<75 nmol/L), and 50% were vitamin D deficient. We found no significant association between vitamin D levels and serum IgE, ECP and obesity in this population of patients with subacute respiratory symptoms.

We conclude that vitamin D deficiency is common in Irish asthma sufferers. Corticosteroid therapy is commonly prescribed for severe asthma and accordingly consideration should be made regarding bone health in patients with airway obstruction.



Poster 9

ETHYL GLUCURONIDE: A marker for alcohol use in methadone maintenance patients.

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Aims:

Methadone maintenance treatment patients provide weekly urines for the detection of drugs & alcohol use. It can be difficult to adequately monitor abstinence from alcohol due to the short half-life of alcohol.

Ethyl glucuronide (EtG) is a direct metabolite of ethanol and can be detected several days after the elimination of alcohol from the body. The aim of this study was to determine the effectiveness of EtG assay in determining alcohol use.

Patients and methods:

The DRI® Ethyl Glucuronide Assay and DRI® Ethanol Assay were supplied by Thermofisher®. These are ready to use homogeneous enzyme immunoassays.

An EtG cutoff of 500ng/mL was chosen above which samples were deemed positive. This allowed a reasonable sensitivity whilst avoiding positive results due to unintentional ethanol exposure.

Urine samples were obtained from 117 participants in a methadone maintenance program. All participants were screened on a regular basis for drug and alcohol use by immunoassay.

Samples were analysed for ethanol and EtG and results recorded.

Results:

Among the initial 117 samples, 33 samples were positive for EtG using the immunoassay testing; however only seven were positive for ethanol.

EtG positive results ranged from 677.5 – 18,606.3ng/mL. The seven alcohol positive results all tested positive for EtG with significantly higher ranges, result were greater than 6,000ng/mL.

Conclusions:

The data recorded from this study indicates the recent alcohol use in thirty three patient samples. Only seven of these screened positive for ethanol use. The detection rate of alcohol use using ethanol assay was calculated at six percent. Using the EtG assay increased this detection rate to approximately twenty eight percent, an increase of twenty two percent.

From these figures it can be concluded that EtG monitoring in methadone maintenance patients for alcohol use can be of significant benefit.

Poster 10

Pyridoxine and Pyridoxal Phosphate Responsive Neonatal Seizure

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Introduction:

Almost all neonatal seizures have a specific cause. Initial evaluations should be directed toward the correctable metabolic and infectious causes since they are the most likely to be amenable to treatment. Hypoxic-ischaemic encephalopathy and structural brain lesions should be excluded by neuroimaging. Rarely, neonatal seizures are associated with the inborn errors of metabolism. It has been suggested that besides inborn errors affecting vitamin B6 metabolism, such as pyridoxine-5-phosphate oxidase deficiency (PNPO) and pyridoxine-dependent epilepsy (PDE), more common epilepsies can also respond to pyridoxine or pyridoxal phosphate treatment.

Case Report:

We present two cases of pyridoxine/pyridoxal phosphate responsive neonatal seizures, both associated with increased levels of threonine in cerebrospinal fluid (CSF), which might be an indication of vitamin B6 deficiency. However inborn errors affecting vitamin B6 metabolism have been excluded by relevant investigations: normal urinary aminoadipic-6-semialdehyde and PNPO mutation analysis.

Case 1: Premature baby girl developed seizures around the time of her birth which correlated with abnormal EEG findings. Extensive investigations were non-contributory. Her CSF threonine was 140 $\mu\text{mol/L}$ (4-45). She received empirical pyridoxine followed by pyridoxal-5-phosphate with marked clinical and EEG improvement.

Case 2: A term baby girl presented at day six with neonatal seizures. They became more frequent over the next three month period and were poorly responsive to increasing doses of antiepileptic drugs. Her CSF threonine was 87 $\mu\text{mol/L}$ (4-45). She has remained seizure-free since pyridoxine treatment was introduced.

Discussion:

Vitamin B6 is not only used in PDE but is also widely used as an adjuvant therapy for seizure control especially if no aetiology is apparent and seizures are poorly responsive to antiepileptic drugs (AEDs). It has been reported that adding pyridoxine to conventional treatment in acute symptomatic recurrent seizures of any cause improved outcome. Some authors have suggested that adding pyridoxal-phosphate to AEDs can help achieve seizure control at lower doses of these drugs. Neonatal seizures form another special group where useful responses can occur. In all these situations pyridoxine and pyridoxal phosphate appear to have an anticonvulsant effect rather than to be treating a metabolic disorder. One bonus of such therapy is the relative lack of side effects.



Poster 11

Fumarate Hydratase Deficiency – Irish Cases and Future Implications for Identification of Carrier Status of this Disorder.

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Introduction: Fumarate Hydratase (FH) deficiency, one of the tricarboxylic acid cycle defects, is an autosomal recessive disorder, characterised by progressive neurologic abnormalities and an isolated increase in fumarate excretion detected on organic acid analysis. It is caused by a mutation in the FH gene located on chromosome 1. Prognosis is related to the severity of the mutation as treatment is largely supportive. Carriers have an increased risk of developing Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome, characterized by multiple benign skin and uterine leiomyomata and aggressive renal cell carcinoma.

Case Report:

Out of ~18,000 urinary organic acid analyses performed over the 5 year period, we found 3 cases with an isolated and persistent increase in fumarate excretion suggestive of FH deficiency. The diagnosis was subsequently confirmed by identification of deficient FH enzyme activity in fibroblasts and molecular genetic testing.

Case 1: A 4 year old girl presented with a history of global developmental delay, particularly with speech and language. Examination revealed microcephaly, increased tone in the lower limbs and ataxic gait. Her mother was a single parent and there were no details on the paternal side of the family.

Case 2: A 3 month old female infant presented with a history of poor feeding, global developmental delay and profound hypotonia. Her maternal uncle had recently been diagnosed with renal cell carcinoma and her mother had a history of uterine fibroids.

Case 3: A 10 year old boy presented with unexplained metabolic acidosis on background of Leigh type encephalopathy. His father died 4 years previously of leukaemia.

Discussion:

Even though FH deficiency is a very rare condition, there are important clinical implications for carriers who are at risk for the development of bilateral aggressive kidney tumours, that tend to spread to lymph nodes and can metastasize early. Early diagnosis greatly improves prognosis. Hence, once the disease-causing mutations are identified, a cascade screening should be considered to identify carriers. The carriers should be offered genetic counselling and assessed for the presence of renal cell carcinoma and subsequently followed up.

Poster 12

Glycogen Synthetase Deficiency: A rare cause of ketotic hypoglycaemia

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Introduction:

Hepatic glycogen synthetase deficiency (GSD0) is a rare autosomal recessive IEM, characterized by fasting ketotic hypoglycaemia. It is caused by mutations in the GYS2 gene located on chromosome 12p12.2. Short stature and osteopenia are common in untreated children, but improve with prevention of hypoglycaemia, lactic acidosis, and ketosis. GSD0 represents less than 1% of all hypoglycaemic cases and the identification of asymptomatic siblings in several GSD0 families suggests that it is under diagnosed. The case described below highlights that while GSD0 is a rare cause of ketotic hypoglycaemia presenting in infancy it should be part of the differential.

Case Report:

A 3 year old girl was diagnosed incidently with ketotic hypoglycaemia when fasting for an MRI brain examination while being investigated for global developmental delay. Blood glucose was 1.5 mmol/L and she had ++++ urinary ketones. She had a history of nocturnal waking, asking for drinks and was sweaty and irritable. On investigation she had no organomegaly or coarse features. While under investigation hypoglycaemia was detected on the ward during routine profiling and pre-breakfast. When hypoglycaemic, urine organic acid and acylcarnitine analysis confirmed ketotic hypoglycaemia with some mitochondrial dysfunction. She had normal blood lactates and low plasma alanines at this time. Post feeds revealed persistent mild hyperglycaemia and hyperlactaemia (~8.5 mmol/L). Urinary excretion of lactate was markedly elevated with mild ketonuria on organic acid analysis. Cortisol, NEFA, insulin and growth hormone responses were appropriate during hypoglycaemia and post prandial. Post glucose challenge, glucose rose to 15 mmol/L and lactate to 5 mmol/L. GSD0 was suspected and confirmed by mutation analysis. She is treated with a high protein diet with complex, low glycemic index carbohydrates to prevent hypoglycaemia and to minimize the systemic acidosis by preventing post-prandial lactic acidosis and fasting hyperketonaemia. Developmentally she is making good progress.

Discussion:

The fasting ketonuria and postprandial hyperglycaemia characteristic of GSD0 should be considered in any child with asymptomatic hyperglycaemia or glucosuria. In patients with GSD0, fasting hypoglycaemia occurs within a few hours after a meal because of limited hepatic glycogen stores and inadequate gluconeogenesis to maintain normoglycaemia. Feeding characteristically results in postprandial hyperglycaemia and glucosuria, in addition to increased blood lactate levels, because glycogen synthesis is limited, and excess glucose is preferentially converted to lactate. If fasting ketotic hypoglycaemia is demonstrated, testing for post-prandial hyperlactaemia should be performed by measuring serial measurements of blood glucose and lactate after a controlled 24h fast or post an oral glucose tolerance test.



Poster 13

Seroepidemiology of the Recent Mumps Virus Outbreaks in Ireland

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Introduction:

Two recent outbreaks of mumps have occurred in Ireland during 2004/2005 and 2008/2009. The aims of this study were to: (a) retrospectively investigate the gender distribution and/or age profile of the infected cohorts and (b) to identify sub-cohorts of individuals who may be maintaining mumps viral infectivity in the Irish population.

Two thousand six hundred cases of acute mumps infection, determined by the presence of mumps-specific IgM were diagnosed by the National Virus Reference Laboratory during the study period. Acute mumps infection occurred more frequently in males than females with a ratio of approximately 2:1 in the 1-9 and 10-19 year old age groups. A 3:2 gender bias, male to female, was observed in the 20-29 year old cohort while the over 30 age group did not demonstrate a gender bias. Serological evidence of prior immunological exposure to mumps virus, as determined by the presence of mumps-specific IgG, was high and similar in males and females in all age groups (93.1% to 100%). A significant increase in the number of acute mumps cases in the ≥ 30 year old age group was observed. This increase was most striking in the post outbreak periods (71.1% in 2007 and 56.2% in 2010).

In conclusion, acute mumps infection demonstrated a significant male gender bias in this study. The consistent and significant increase of mumps infection in the ≥ 30 year old age group, evident in the post outbreak periods, suggest that this cohort may be responsible for maintaining mumps viral infectivity and hence periodic outbreaks in the Irish population.

Poster 14

Epstein-Barr Virus Gene Expression, Human Leukocyte Antigen Alleles and Viral Loads in Paediatric Renal Transplant Patients.

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Introduction:

Primary infection with Epstein-Barr virus (EBV) usually occurs at a young age and is generally asymptomatic. Thereafter the virus persists for life in a latent genomic form within B lymphocytes. Studies have identified solid organ transplant recipients who remain asymptomatic despite maintaining chronic high levels of EBV. In this study we examined clinical manifestations, EBV gene expression and "viral load", human leukocyte antigen (HLA) alleles and specific T-cell responses to EBV infection in paediatric renal transplant patients.

Seventeen paediatric renal transplant patients were categorized according to EBV "viral load" into those with persistent chronic high "viral loads" (CHL, n=8) and those recipients who resolved EBV infection (REI, n=9). EBV gene expression was analyzed using real-time PCR. EBV-specific T cells were analyzed by specific pentamer staining and flow cytometry.

EBV-encoded small RNA 1 was expressed at significantly higher levels in the CHL group compared with REI group ($p < 0.07$). BamHI A right-ward transcripts were also expressed at higher levels in CHL patients ($p < 0.03$). Expression of latent genes, EBNA1, LMP1, LMP2 and lytic gene BZLF1 were restricted to the CHL group with viral gene expression varying over time. HLA-A*02 allele expression was predominant in CHL patients (80%). However, GLC lytic-specific cytotoxic T-lymphocytes were absent in CHL patients. HLA-B*08 allele expression was prevalent in REI patients (71%). RAK lytic cytotoxic T-lymphocytes were detected at similar levels in all patients.

EBV gene expression in patients with chronic high "viral loads" differs from those that resolve infection and should be interpreted alongside HLA polymorphisms. Our findings suggest an association between HLA-A*02 allele, EBV gene expression and chronic high EBV viral load carriers in paediatric renal transplant recipients.



Poster 15

Is the Measurement Epstein Barr Virus Early Antigen IgG of Diagnostic Value?

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^bNational Liver Transplant Unit, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

Introduction:

Currently, Epstein-Barr Virus DNA is quantified by PCR to provide a measure of the “viral load” and this parameter helps identify patients at risk of developing post-transplant lymphoid tumours. The Epstein-Barr Virus early antigen (EBV EA) complex consists of multiple proteins with potential significance for diagnosis of EBV related disease. The primary objective of this study was to examine the potential diagnostic role of EBV EA IgG in: (a) immunocompromised adult liver transplant recipients at risk of developing post-transplant lymphoproliferative disorders (PTLD) and (b) individuals with infectious mononucleosis exhibiting an atypical antibody response. A secondary objective was to compare the performance of three commercially available assays for serum EBV EA IgG.

A panel of sera from 28 liver transplant recipients and 41 additional patients with suspected or confirmed infectious mononucleosis were tested for EBV EA IgG using 3 commercial assays: (1) a manual ELISA, (2) an automated indirect chemiluminescence immunoassay (CLIA) and (3) a reference immunoblot assay.

The presence of EBV EA IgG correlated with EBV DNA viral load for all three assays. However, the CLIA assay was more accurate and more sensitive with respect to the reference immunoblot assay and had a significantly faster turnaround time for the detection of EBV EA IgG than the ELISA assay. The presence of EBV EA IgG was found in 72% of patients with confirmed infectious mononucleosis. There may be a role for EBV EA IgG testing, in conjunction with EBV viral load measurement in identifying immunocompromised transplant recipients at higher risk of developing PTLD. However, EBV EA IgG measurement does not play a significant role in the differential diagnosis of EBV infection in immunocompetent individuals.

Poster 16

An Audit of the Number & Frequency of Unacceptable Specimens & Review of Reasons for Rejection within the Biochemistry Laboratory

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Introduction:

Sample rejection is both time consuming and inconvenient to the patient and may delay diagnosis or management decisions. Clinical laboratories must improve the pre-analytical phase, a phase that is highly susceptible to mistakes. The aim of this audit was to identify the main reasons for specimen rejection and highlight areas in which improvements could be sought, to reduce the need to redraw blood and lessen patient discomfort and improve turnaround time.

124,652 specimens were received into the Biochemistry laboratory over a 3 month period from wards, ICU, ED, OPD and GP's. There were 933 rejected specimens for this period (0.75% of the total). The rejected specimen were categorised by reason of rejection and also by location. The most common reason for rejection of specimens was haemolysis (761 of 933, 81%). The second most common cause was mislabelling of specimens. Other common causes included insufficient specimen and delayed receipt of specimen. ED had a high rate of haemolysed specimens, whereas ICU had very few.

Conclusions:

Haemolysis and mislabelled specimens are by far the most common cause of specimen rejection. Haemolysis was more common in areas such as ED, with a constant turnover of teams, and uncommon where blood is taken from indwelling lines, such as in ICU.

Preventative actions:

A programme of phlebotomy training for non-phlebotomy staff was put in place in ED and order of draw charts were issued. The objectives were to assist in the reduction of the number of haemolysed specimens and mislabelled specimens that cause the patient to be bled again with increased turnaround times and thus to help in achieving the patient safety goal of correct procedures.



Poster 17

Neutrophil function assessed by Pholasin® based bioluminescence assay. Results of a pilot study.

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² Knight Scientific Limited, Plymouth, UK.

³ Independent Consultant Physiologist

Introduction:

Neutrophils play a pivotal role in immune defence. Myelodysplastic syndrome (MDS) is variably associated with quantitative and qualitative neutrophil abnormalities. Quantitative estimation of neutrophils is the only routine tool available to clinicians to monitor treatment of MDS(1). Studying functional heterogeneity of circulating neutrophils has potential as a clinical tool(2). The ABEL (Analysis By Emitted Light) cell activation assay using the light emitting protein Pholasin® measures subtle changes in neutrophil response to mediators of infection and inflammation. Therefore neutrophil response to activation may be assessed by measuring this response. It is hypothesised that assessment of Pholasin® bioluminescence may reflect neutrophil dysfunction in MDS.

Materials and Methods:

10 patients with MDS and 10 "Normal" individuals were recruited. Total white cell count and cell differentiation were assessed using a Sysmex analyser. Neutrophil function was assessed using the Knight Scientific ABEL cell activation kit according to manufacturer's instructions. The kit contains the unique light-emitting Pholasin® as well as the cell stimulants phorbol-myristate-acetate (PMA) and formyl-methionyl-leucyl-phenylalanine (fMLP).

Results:

Control samples show a clear response to stimulation with a typical "Normal" cell activation plot: clear peak and trough activity for the cell suspensions with no residual activity in the blank preparations. MDS patient samples (Fig. 3&4) show a flat response when stimulated. Unexpected increasing activity, with time, was detected in the blank preparations.

Discussion:

The control samples, when stimulated with either fMLP or PMA, show clear stimulation responses. MDS patients show no such response indicating they have abnormal neutrophil function. This pilot study suggests Pholasin® based ABEL analysis may prove useful in assessing neutrophil function in MDS. Further research is ongoing to elucidate the full meaning and value of these findings.

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Poster 18

Profound High Bone Turnover in X-Linked Hypophosphataemic Rickets with very “Hungry Bones” following Total Parathyroidectomy.

**O’Keane M, Kilbane M, Crowley R, McKenna MJ, Cunningham SK.
Metabolism Laboratory and Department of Endocrinology, Clinical chemistry Group of laboratories,
St. Vincent’s University Hospital, Dublin 4.**

Introduction:

An eighteen year old woman presented in 1994 with X-linked hypophosphataemia (XLH) complicated by tertiary hyperparathyroidism: parathyroid hormone (PTH) level 251 ng/L (reference range: 12-64) and ionised calcium (Cai) level 1.38 mmol/L (reference range: 1.19-1.35) in conjunction with Vitamin D (25(OH)D) deficiency 15.4 nmol/L (threshold for sufficiency >50 nmol/L). PTH and Cai rose steadily over the next 17 years in the presence of normal 25(OH)D levels. Cinacalcet lowered Cai but there was paradoxical rise in PTH. Patient had a total parathyroidectomy (PTX) in 2011.

Tubular resorption of phosphate was consistently low (range 0.18-0.59 mmol/L, normal range 0.84-1.48 mmol/L). Genetic screening in 2009 identified a novel deletion (T nucleotide)/insertion (GG nucleotides) in exon 22 of the PHEX gene that resulted in a premature termination at codon 725.

Bone turnover markers in 1999 demonstrated increased levels of formation; serum bone-specific alkaline phosphatase (bone ALP) was 67 (reference range 6.1-11.8 µg/L), serum intact osteocalcin (OCI) was 91.8 (reference range 9.7-18.1 µg/L), and procollagen type I N-propeptide (PINP) was 234.5 (reference range 27.2- 71 µg/L). Urinary N-terminal crosslinking telopeptide of type I collagen (uNTX), a marker of bone resorption was 150.5 (reference range 25.5-72.4 nMBCE/mMCr). From 2000-2010 a marked rise occurred and, pre PTX, bone formation markers were; OCI 548 µg/L, PINP 6,604 µg/L, bone ALP 651 µg/L. Pre PTX bone resorption markers were; uNTX 4,623 nMBCE/mMCr, and the C-terminal crosslinked telopeptides of type I collagen (sCTX-1) 8.3 (reference range 0.025-0.573 µg/L). Post PTX, PTH declined to <6.0 ng/L that preceded a marked decrease in bone resorption markers and a later decline in bone formation. Refractory hypocalcaemia developed post operatively that required intravenous calcium infusion for over 4 months due to “hungry bones”.



Poster 19

Evaluation of Elecsys Troponin T hs (High Sensitive) Assay versus Troponin T 4th Generation Assay on the Roche Modular Analytics E170

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Introduction:

High-sensitivity cardiac troponin assays have recently been introduced into clinical laboratories to aid the earlier diagnosis of acute myocardial infarction (AMI). We evaluated the analytical performance of the Elecsys Troponin T hs Assay versus Elecsys Troponin T 4th Generation Assay on the Roche Modular Analytics E170.

Methods:

Patient samples were analysed on 2 separate Roche E170 analysers using Elecsys Troponin T hs, versus Elecsys Troponin T 4th Generation. More than 400 specimens were analysed by both methods. Results were compared within clinical context. Imprecision was assessed using commercially available Quality Controls and also in pooled patient samples prepared at a range of low levels (~3ng/L to ~13ng/L). Bias was also assessed using EQA specimens.

Results:

Imprecision

Within-run imprecision ranged from 2.6% at 16 ng/L, to 0.94% at 2122 ng/L.

Between-run imprecision ranged from 9.1% at 15 ng/L, to 7.0% at 1027 ng/L.

Patient Pools (low values):

Mean imprecision from both analysers was 2.3% for a pool with a mean value of 13 ng/L and 9.0% at a mean value of 4.4 ng/L (intermediate values: 4.7% at 7.3 ng/L and 3.8% at 5.6 ng/L).

Comparison of two analysers (Line 1 and Line 3):

There was no significant difference between TnT hs values on Line 1 and 3, when 57 patient specimens with detectable TnT hs values were compared, using Bland-Altman analysis with t- test.

Comparison of TnT hs with TnT Values for Patient Specimens:

More than 400 specimens were analysed by both methods. No specimens with raised TnT values ($>0.03 \mu\text{g/L}$) had normal values with TnT hs assay. All specimens with TnT hs $> 50 \text{ ng/L}$ had values $\geq 0.03 \mu\text{g/L}$ by the TnT assay. Many specimens with TnT values $< 0.03 \mu\text{g/L}$ had raised values ($>14 \text{ ng/L}$) with the TnT hs assay. This is consistent with the manufacturer's claims and reports by others, that the high sensitivity assay identifies more patients with less marked myocardial injury.

Conclusion

Performance of the TnT hs assay is considered very satisfactory in terms of low imprecision, and good comparison between two analysers. The comparison with TnT Values was as expected and confirmed the manufacturer's claims and previous reports. We confirmed that imprecision was $<10\%$ at the 99th percentile of the reference range (14ng/L). In conclusion, Troponin T hs will likely aid the earlier diagnosis of AMI. The improved sensitivity of the assay is potentially of great diagnostic and prognostic value, not only in patients with acute coronary syndromes, but also in stable patients with a variety of cardiac disorders.

Poster 20

Enzymatic creatinine assay is preferable to Jaffe assay for monitoring renal function in patients being treated with Cefoxitin

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Introduction:

Cefoxitin, a cephalosporin antibiotic, has been shown to cause positive interference in Jaffe creatinine assays but not in enzymatic creatinine assays. A Cystic Fibrosis patient was commenced on Cefoxitin therapy together with Amikacin, which necessitated monitoring of renal function. The patient's creatinine concentration was measured by the methods above with results from the enzymatic creatinine method only being reported.

Aim:

The aim of the study is to establish the extent of interference by Cefoxitin and other cephalosporins in the measurement of creatinine by the Roche Jaffe assay.

Method:

Creatinine was measured on the patient's plasma samples and on drug free plasma samples (n=5) using the Roche Jaffe (SVUH) and Roche enzymatic (Rotunda Hospital) creatinine assays. Creatinine, using the Jaffe assay, was measured in drug free plasma samples with three creatinine concentrations: 76, 184 and 460 μ mol/L, which had been spiked with Cefoxitin in the following concentrations: 100, 250, 1000 and 2000mg/L, representing documented therapeutic levels. Interference by three other cephalosporins, Ceftazidime, Cefotaxime and Cefuroxime in the Jaffe assay, was also studied.

Results:

The mean creatinine measurements of the five drug free plasma samples, showed no significant difference between the two assays: (Mean Jaffe creatinine 49.8 \pm 4.0 μ mol/L; Mean Enzymatic creatinine 46.2 \pm 2.3 μ mol/L; p=0.0625).

The patient's creatinine results differed significantly (Mean Jaffe creatinine 62.3 \pm 9.6 μ mol/L; Mean Enzymatic creatinine 48.8 \pm 5.2 μ mol/L; p=0.0431)

Plasma spiked with Cefoxitin showed positive interference (range: 4.3-211% increase) in the measurement of creatinine by the Jaffe assay at all drug concentrations > 250mg/L. This was most pronounced in plasma of normal creatinine concentration (range: 17-211%). Cefotaxime and Cefuroxime showed no interference, while Ceftazidime showed positive interference of 18% at 5000mg/L.

Conclusion:

Falsely elevated creatinine concentrations were observed, in a patient on Cefoxitin therapy, using the Roche Jaffe assay. A lesser degree of interference was seen with Ceftazidime. The renal function of patients treated with Cefoxitin should be monitored using the enzymatic creatinine assay.





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