INTRODUCTION

Welcome to the 19th annual Austin LifeSciences Research Week. Once again we take time out to recognise and celebrate the quality and the breadth of the research being performed on this site through Austin health and its departments, its affiliated universities and research institutes, and also Mercy Hospital for Women. It is a time when people can share experiences and set up new collaborations, and to think towards the future in terms of cooperative grant applications, attracting future students and scientists, and cementing our place as one of the leading research centres in Australia. The research culture at Austin is vibrant and part of what we do every day. Already this is leading to changes in health care policy and practice and ultimately to better health outcomes for all of us.

Once again the Research Week Committee has considered your feedback very carefully and made changes to the format. Not all of the suggestions were physically possible or even legal, and certainly not without appropriate ethics approval! In 2011 we had a record number of abstracts submitted leading to unprecedented challenges in terms of how to accommodate everyone. We recognise that not every solution is perfect for everyone and we will gratefully consider suggestions for future years, once any packages have been cleared by the bomb squad.

In 2011 we have:
• continued the format of two separate poster sessions;
• provided a significant number of opportunities for researchers to present their work orally during the mini-oral sessions;
• continued the RJ Pierce Symposium, an event first held in 2009 to honour the contribution of the late Professor Rob Pierce;
• instituted a Research Week debate that will be both entertaining and thought-provoking.

Other successful initiatives such as the Professors Professing seminar are also continuing. Several excellent abstracts have been chosen for oral presentation and will be competing for a substantial prize at the Austin LifeSciences Symposium. We are fortunate to have a streamlined and professional abstract submission and assessment system, thanks to sponsorship by ASN Events.

Our plenary session this year is highlighted by Professor Ian Everall, MBBS (Hons), Ph.D, FRCPSYCH, FRANZCP, Cato Chair and Head of Department of Psychiatry, University of Melbourne. His presentation is entitled, "Back to the Future - What have we Learned about Psychosis and its Cellular and Molecular Changes in the Last 100 Years?" As always, the Research Week awards will also be presented at the plenary session. Make sure you lock all these exciting events into your diaries.

We thank all of our new and returning sponsors, without whom Research Week would not be possible.

I hope you find Austin Health Research Week 2011 to be most interesting and enjoyable.

A/Prof Ian Davis
Chair
Austin LifeSciences Research Week Committee
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Austin LifeSciences Research Week gratefully acknowledges the generous support of these sponsors in 2011

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AUSTIN HEALTH RESEARCH WEEK PRIZES 2011

LUDWIG INSTITUTE SCHOLARSHIP
Up to $1000 to be used towards travel to a scientific meeting in Australia

FLOREY NEUROSCIENCES INSTITUTE PRIZE
$1000 towards costs to attend a scientific meeting

AUSTIN LIFE SCIENCES PRIZE FOR BASIC RESEARCH
$1000 towards costs to attend a scientific meeting

ALLIED HEALTH RESEARCH AWARD
$750 towards costs to attend a national research meeting

NURSING RESEARCH AWARD
$750 towards costs to attend a research meeting

NURSING ENCOURAGEMENT AWARD
$500 towards further education professional development or nursing research

ROB PIERCE MEMORIAL AWARD
$1000 as a grant-in-aid, to be used for research related purposes

PIRI EARLY YEARS AWARD
$200 towards costs of attendance at a scientific meeting

BEST COMMUNICATION POSTER AWARD
For the poster judged to communicate the message most effectively

THE sanofi-aventis PRIZE FOR CLINICAL RESEARCH IN ENDOCRINOLOGY
$1000 towards costs to attend an overseas scientific meeting

THE sanofi-aventis PRIZE FOR CANCER RESEARCH
$1000 towards costs to attend an overseas scientific meeting

GlaxoSmithKline PRIZE FOR SCIENTIFIC RESEARCH
Two identical prizes of $3,000 reimbursement of costs associated with attendance at a scientific meeting or course

GlaxoSmithKline YOUNG RESEARCHER AWARD
$4,000 reimbursement of costs associated with attendance at a scientific meeting or course

AUSTIN MEDICAL RESEARCH FOUNDATION Young Investigator Award
$2,500 towards costs to attend a national or international scientific meeting or professional development course

AUSTIN MEDICAL RESEARCH FOUNDATION Distinguished Scientist Award

All winners will be announced at the Research Week Plenary Session, Thursday 20 October 2011.
Certificates will be presented by our guest lecturer, Professor Ian Everall, MBBS (Hons), PhD, FRCPsych, FRANZCP, Cato Chair and Head of Department of Psychiatry, University of Melbourne
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Program 2011

Monday 17 October 2011
Lunchtime forum 12 noon - 1pm John Lindell lecture theatre
Professors professing - Recent recipients of AHMRF Distinguished Scientist Award
Prof Mary P Galea (2010 winner), Prof Arthur Shulkes (2004 winner) followed by lunch

Mini oral sessions 2-4 pm Education Precinct L4 Austin Tower
Concurrent mini-oral sessions featuring the work of junior research staff.
Sessions occurring:
2 - 3.30pm Nursing: Rm 4.6
2 - 4pm Respiratory and Sleep Medicine: Education Ctr Lecture theatre
2 - 3pm Ludwig Institute: John Lindell Lecture theatre

Tuesday 18 October 2011
Lunchtime Debate 12 noon - 1pm John Lindell lecture theatre
Debate
“Lab or Clinic? That research funds are better spent on reducing waiting lists”,
Affirmative: Prof Jeffrey Zajac, Ms Kim O'Sullivan, Prof Graeme Jackson
Negative: Prof Rinaldo Bellomo, Prof Neville Yeomans, Dr Jennifer Johns
Moderator: Dr Brendan Murphy
followed by lunch

Poster session; Group I categories 2.30 - 3.30pm
Level 4 Austin Tower, Education Precinct rooms 4.4 and 4.5

Wednesday 19 October 2011
Austin LifeSciences Symposium 12 noon - 1.30pm John Lindell lecture theatre
Austin Medical Research Foundation Young Investigator Award Finalists present their work, followed by lunch

Friday 21 October 2011
RJ Pierce Symposium 12 noon - 1pm, John Lindell Lecture Theatre, followed by lunch.
The symposium will comprise four 10-minute presentations, followed by a panel discussion chaired by Associate Professor Mal Hopwood;
A/Prof James Olver - New Insights into the Pathophysiology of Obsessive Compulsive Disorder
A/Prof Trevor Norman - Stress and Performance
A/Prof David Castle - Anorexia Nervosa Treatment; Evidence Based or Evidence Generating?
A/Prof Mal Hopwood - Mental Health Outcomes from the Victorian Bushfires

Thursday 20 October 2011
Plenary session 12 noon - 1.15 pm John Lindell Lecture theatre
Speaker: Professor Ian Everall, MBBS (Hons), Ph.D, FRCPSYCH, FRANZCP, Cato Chair and Head of Department of Psychiatry, University of Melbourne.
“Back to the Future - What have we Learned about Psychosis and its Cellular and Molecular Changes in the Last 100 Years?”
Awards Presentations
followed by lunch

Poster session; Group 2 categories 2.30 - 3.30pm
Level 4 Austin Tower, Education Precinct rooms 4.4 and 4.5

Wednesday 19 October 2011 (cont’d)
Austin by Design Showcase Event 2011
1.30 - 4.00 pm
Education Precinct Lecture theatre and breakout area
The Austin by Design Showcase event is a great opportunity to share improvements of patients and staff experiences with the broader Austin Health community
Tuesday, 18 October 2011

Poster session; Group I categories
2:30 PM - 3:30 PM  Level 4 Austin Tower, Education Precinct rooms 4.4 and 4.5

Anaesthesia

Philip Peyton
Continuous Non-invasive Perioperative Monitoring of Cardiac Output by Pulmonary Capnotracking  abs#001

Philip Peyton
Investigation of ventilation-perfusion scatter in the lung during anaesthesia using the MIGET  abs#002

Cardiology

Ali Al-Fiadh
The Presence of Retinal Microvascular Dysfunction is a Predictor of Underlying Coronary Artery Disease  abs#003

Ali Al-Fiadh
Effect of Venous Pressure on Fractional Flow Reserve and Index of Microcirculatory Resistance in Patients with Stable Chest Pain Syndromes  abs#004

Leighton Kearney
Global Longitudinal Strain is a strong independent predictor of all-cause mortality in patients with Aortic Stenosis  abs#005

Leighton Kearney
Utility of cardiac magnetic resonance imaging for the assessment of prosthetic aortic valves  abs#006

Sheila Patel
Association of ACE2 genetic variants with blood pressure, left ventricular mass and cardiac function in Caucasians with type 2 diabetes.  abs#007

Sheila Patel
Left ventricular hypertrophy in type 2 diabetes; effect of indexing to height versus body surface area on prevalence and cardiovascular events.  abs#008

Janet Chen
Evaluation of Right Ventricular Volume and Systolic Function - A Comparison of 2 and 3-Dimensional Echocardiography with Cardiac Magnetic Resonance  abs#009

Ying Yan Zhu
Lipid Exposure Enhances Arterial Graft Patency via the Native Vessel Pathway: An Illustration of the Competitive Flow Phenomenon After Coronary Surgery  abs#010
Cardiology (cont’d)

**Fahd Chahadi**

Electrical Characteristics of Multipolar Left Ventricular Pacing Leads  
[abs#011]  
Fahd Chahadi

Super-responders to Cardiac Resynchronisation Therapy (CRT)  
[abs#012]  
Fahd Chahadi

5 year experience with CRT in a multidisciplinary service.  
[abs#013]  
Fahd Chahadi

Shock reduction in implantable cardioverter defibrillators - A local perspective  
[abs#014]  
Trong Nguyen

Characterisation of native vessels disease in coronary artery bypass graft patients  
[abs#015]  
Konstantinos Profitis

Tricuspid Regurgitation is an Independent Predictor of Mortality in Acute Pulmonary Embolism  
[abs#016]  
Hui-Chen Han

Cardiac rhythm monitoring. Are we missing the beat?  
[abs#017]  
Terase Lancefield

Is obesity a risk factor for adverse outcome following coronary artery bypass graft surgery (CABG)?  
[abs#018]  
Terase Lancefield

Angiotensin converting enzyme 2 (ACE2): a novel marker of coronary artery disease in Man  
[abs#019]  
William Shi

Does the addition of a radial artery graft improve survival after higher risk coronary artery bypass grafting? A propensity-score analysis of a multicentre database.  
[abs#020]  

Critical Care & Emergency Medicine

**David Taylor**

IV droperidol or olanzapine as adjuncts to midazolam for the acutely agitated patient: a multi-centre, randomised, double-blind, placebo-controlled, clinical trial  
[abs#021]  
David Taylor

Meeting a simple clinical target results in a high level of patient satisfaction with their pain management  
[abs#022]  
David Taylor

Obesity has few adverse effects on the patients’ experience in the Emergency Department  
[abs#023]  
David Taylor

Public Health screening in the Emergency Department: An extra dimension  
[abs#024]
Critical Care & Emergency Medicine (cont’d)

Glenn Eastwood
Arterial oxygen tension and mortality in mechanically ventilated patients  
Glenn Eastwood
Haemodynamic impact of a slower pump speed at start of CRRT  
Neil Glassford
Renal biomarkers may be of limited utility in the general intensive care population.  
Neil Glassford
NGAL as a marker of tubular damage appears to be unrelated to FENa as a marker of tubular function in patients with AKI.  
Neil Glassford
Urinary hepcidin is a marker of systemic inflammation in the setting of preserved kidney function.  
Neil Glassford
FENa is not a useful renal biomarker in the critically ill.  
Neil Glassford
Neutrophil Gelatinase-Associated Lipocalin (NGAL) has a stronger correlation with serum creatinine than c-reactive protein.  
Antoine Schneider
Renal perfusion evaluation by contrast ultrasound after cardiac surgery, a pilot study  
Antoine Schneider
Severe acute kidney injury NOT TREATED with Renal Replacement Therapy: Characteristics and outcome  
Antoine Schneider
Comparison between fluid balance and changes in body weight in the critically ill patient  
Dr Michael Yeoh
An audit of analgesia practices for fractured neck of femur patients in the Austin Health emergency department  
Ian Baldwin
Development of a web based portal for recording and reviewing postgraduate nursing experience in ICU.  
Michael Yeoh
An audit of wrist fracture management in The Austin Health emergency department  
Michael Yeoh
An audit of appendicitis management in The Austin Health Emergency Department
Geriatrics

Sandra Iuliano-Burns
Sarcopenia and Vitamin D Deficiency are Risk Factors For Falls But Remain Undetected in Aged Care Residents

Cilla Haywood
Safe, effective use of a very low energy diet in an obese elderly inpatient.

Immunology

Damien Zanker
The immunoproteasome is expressed by lymphocytes and plays critical roles in lymphocyte development

Damien Zanker
Systematically exploring the contribution of individual immunoproteasome subunits to influenza cd8+ t cell repertoire and epitope abundance

Damien Zanker
An optimised culture method for establishing murine cd8+ t cell lines

Damien Zanker
Broad cross reactivity of CD8+ T cells obscures epitope identification

Kok-Fei Chan
Polyclonal T-cell Receptors Recognise an Unusually Long Tumour Antigenic Peptide Complexed to HLA-B7

Jason Waithman
The initiation of the cellular immune response to cutaneous melanoma

Infectious Diseases

Natasha Holmes
Increased Mortality in Patients with S. aureus Bacteremia Isolates with Elevated Vancomycin Minimum Inhibitory Concentration (MIC) Persists After Adjustment for Comorbidities.

Natasha Holmes
Vancomycin Pharmacodynamics in Staphylococcus aureus Bacteremia (SAB).

Andrew Mahony
Marked reductions in rates of vancomycin-resistant enterococci (VRE) colonisation & disease associated with introduction of a routine hospital-wide bleach cleaning program

Janet Montgomery
Validation of new BinaxNOW Staphylococcus aureus and PBP2a tests performed directly from Blood Cultures
Infectious Diseases (cont’d)

Janet Montgomery
Fosfomycin Susceptibility of Multi-Resistant Bacteria by ADS and Etest

Patrick Charles
Is doxycycline equivalent to macrolides when combined with beta-lactams for the treatment of Community-Acquired Pneumonia?

Patrick Charles
Improving ordering of C-reactive protein (CRP) testing at Austin Health - an Austin by Design project

Joseph Torresi
Hepatitis B virus induces loss of cIAP1 and sensitivity to TNF-alpha in primary hepatocytes

Joseph Torresi
Deregulation of hepatocyte signal transduction, cIAP1 and apoptosis by hepatitis C virus.

Doug Johnson
Hepatitis C virus-like particle vaccines with novel adjuvants produce strong neutralising antibody and T cell immune responses in MHC Class I transgenic mice

Bradley Gardiner
Inducible resistance to clindamycin in Staphylococci: Validation of Vitek-2 against CLSI D-Test

Medical Imaging

Miranda Siemienowicz
This Poster is Non-Diagnostic: Quality assurance in computed tomography pulmonary angiography

Elissa Botterill
Meningioma: Radiologic-Pathologic Correlation

Kevin Ong
Conversion from Mild Cognitive Impairment to Alzheimer’s Disease: Predictive value of Aβ imaging with 18F-Florbetaben

Natalie Tavare
Phantom Evaluation of PET Attenuation Correction Using Computed Tomography in Presence of Contrast Agent

Michael Yeoh
An audit of CT brain (CTB) ordering within The Austin Health Emergency Department

Evelyn Laurens
Synthesis and biological evaluation of novel fluoro-18 labelled Positron Emission Tomography (PET) imaging agents for hypoxic tissues in tumours

Uwe Ackermann
Implementation of an in vitro assay for phase 1 metabolism of PET radiotracers.
Medical Imaging (cont’d)

Shinn Dee Yeoh
Automated production of \([^{18}\text{F}]2\)-fluoroethyl azide and a thymidine analogue using the Synthera module

Musculoskeletal

Lionel Schachna
Long-term drug survival of anti-TNF therapy in ankylosing spondylitis

Russell Buchanan
Body mass index and large joint involvement in rheumatoid arthritis

Sandra Iuliano-Burns
Improving Management of Low Trauma Fractures in a Tertiary Hospital. The “Fracture Capture” Project

Occupational therapy

Melissa Hirth
Early return to work and improved range of motion with modified relative motion splinting (mRMS): A retrospective comparison with immobilisation splinting for zones V & VI extensor tendon repairs.

Tamara Tse
A systematic review of participation measures post-stroke.

Leanne Carey
SENSSe: Study of the Effectiveness of Neurorehabilitation on Sensation: Individual patient characteristics that predict favourable outcomes.

Anne Marie Tan
SenScreen - Sensory Screening Stroke Study: Development and Implementation of a standardised sensory screening tool for use with sub-acute patients post stroke.

Kay Russell
The impact of Frontotemporal lobar degeneration on driver performance.

Joanne Cairney
Occupational Therapy and liver transplantation: Exploring the scope of practice.

Amanda Bladen
Evidence Based Supervision,: a best practice model of supervision, based on the voice and insights of occupational therapists and grounded in evidence.
Oncology & Haematology

Werança Ranasinghe
Hypoxia inducible factor 1α (HIF1α) causes poor response to Chemotherapy in Androgen Independent Prostate Cancers (AIPC)

Angelo Perani
Evaluation of an online biomass probe to monitor cell growth and cell death

Ingrid Burvenich
Optimizing pharmacokinetics and targeting properties of recombinant anti-Lewis Y antibody hu35193 in A431 tumor-bearing mice

Dianne Legge
Innovations in supportive care practice: the Brain tumour Support Officer at Austin Health

Negar Shahmoradi
Nutritional Status, Complementary and Alternative Medicine Use and Nutritional Support of Cancer Patients in Hospice Home Care

Aparna Jayachandran
Mechanism of epithelial-to-mesenchymal transition in metastatic melanoma

Natalie Turner
Association of CT antigen expression and survival in stage III melanoma.

Nigel Anderson
IMRT for Oropharyngeal Carcinoma: Improving Acute Dysphagia and Post Treatment Weight Management through Superior Midline Sparing During Definitive Chemo-Radiation.

Mun Sem Liew
Pathologic responses to gemcitabine/platinum-based neoadjuvant chemotherapy for muscle-invasive urothelial bladder cancer

Andreas Behren
EMT in melanoma is characterized by upregulation of TSP-1

Prahlad Ho
An Intensified Conditioning Regiment With Intravenous (IV) Busulphan-Melphalan (Bu-Mel) And Pharmacokinetic (PK) Monitoring Prior To Autografting For Poor Prognosis Non-Hodgkin Lymphoma (NHL)

Prahlad Ho
CNS Multiple Myeloma (MM) - a Multicentre Experience of a Rare Manifestation

Prahlad Ho
Intermittent Granulocyte-Colony Stimulating Factor (G-CSF) Maintains Dose Intensity After ABVD Therapy Complicated By Neutropenia

Prahlad Ho
High-Dose Methotrexate For The Treatment Of Relapsed Central Nervous System (CNS) Erdheim Chester Disease (ECD)

Bee Tan
FOXP3 overexpression inhibits growth of melanoma cells in vitro
Oncology & Haematology (cont’d)

Pu-Han Lo
Generation of a melanoma resource database  [abs#091]

Sharon Gibbs
Intrafraction Prostate Movement and the Zero Action Threshold  [abs#092]

Anderly Chueh
Sustained IE gene induction is linked to HDACi-induced apoptosis in multiple tumour types [abs#093]

Tricia Wright
Investigating the Use of a Pre-operative Haematinic Screen in Cardiac Surgery Patients [abs#094]

Sujitra Detchokul
Complex protein interaction networks of CD151-promoted cell motility and metastasis in prostate cancer: A systems biology analysis [abs#095]

Elham Amini
Ki67 expression in oestrogen receptor positive breast ductal carcinoma [abs#096]

Tricia Wright
Diagnosis and management of acquired haemophilia A in a major teaching hospital in Melbourne, Australia: Review of 5 cases. [abs#097]

Andreas Behren
Epigenetic modulation of tumour targets for enhanced immunotherapy of cancer [abs#098]

Yvonne Yeung
A survey of Taxotere-Cyclophosphamide-Herceptin (TCYCH) chemotherapy use and safety profile in HER-2 positive breast cancer patients in Australia [abs#099]

Pavel Sluka
The Effect of Microenvironmental Factors on the Biology of Primary Prostate Cancer Cells in vitro [abs#100]

Genevieve Whitty
Characterisation of Primary Prostate Cancer Cells in vitro [abs#101]

Malcolm Feigen
Controversies in the management of malignant pleural mesothelioma: the case for conservative surgery and high-dose hemithoracic radiotherapy [abs#102]

Dixon (Teck Sing) Woon
Characterisation of immune infiltrates in malignant and benign prostate tissues [abs#103]

Kelly Mills
Screening for supportive care needs at commencement of cancer treatment [abs#104]

Glenn Cartwright
Tumour targeting of the anti-EphA3 antibody, chIIIA4, reduces tumour burden and effects vasculature of human prostate cancer tumour xenografts [abs#105]
Oncology & Haematology (cont’d)

Janson Tse
Mechanisms underlying the synergistic apoptotic activity of HDAC and proteasome inhibitors in colon cancer cells.

Matthew Anaka
A subpopulation of slow cycling, invasive and therapy resistant melanoma cells identifies EMT-like processes in melanoma

Damien Zanker
Flt3 ligand expands FoxP3+CD4+ regulatory T cells in human subjects

Laura Vella
CD133 expression on the surface of melanoma cells is paralleled by coordinated changes in gene-expression

Christopher Hudson
Identifying extracellular therapeutic targets on melanoma cells

Nhi Huynh
PAK1-Knockdown Suppresses Proliferation and the Epithelial-Mesenchymal Transition (EMT) in vitro & in vivo.

Physiotherapy

Plaiwan Suttanon
Balance and mobility dysfunction, and falls risk in older people with mild-moderate Alzheimer’s disease

Phuong Phan
Community mobility relates to walking speed post stroke

Jannette Blennerhassett
Mobility and falls after discharge from stroke rehabilitation

Chris Cimoli
Evidence Based Practice (EBP) in Rehabilitative Physiotherapy

Frances Batchelor
Does fear of falling increase after falls in people with stroke?

Leanne Rees
The natural history of weight change following a spinal cord injury. A longitudinal, observational study.

Ro Packer
A Review of Benign Paroxysmal Postititional Vertigo (BPPV) in Patients Admitted to the Acquired Brain Injury (ABI) Unit at Royal Talbot.

Kimberley Haines
Delayed mobilisation is associated with increased risk of post-operative pulmonary complications following high risk upper abdominal surgery

Luis Cofre
Ankle plantar-flexor power in human gait.
Physiotherapy (cont’d)

Luis Cofre
Speed effect on joint powers in ageing gait.  

Clare Nash
Assessing acute aged-care patients for their risk of falls in the community prior to discharge  

Danielle Di Natale
OA Hip and Knee Service  

Kimberly Miller
The F-AsTex: a new tool for measurement of tactile discrimination of the foot.  

Catherine Granger
Self reported physical activity levels, fitness and muscle strength of people with non-small cell lung cancer: preliminary analyses.

Renal

Karen Manley
Taste Changes in Renal Failure  

Matthew Roberts
Cardiac Troponin T as a predictor of long term mortality in patients undergoing haemodialysis  

Darren Lee
Failure of proteolysis as a novel mechanism for tubular proteinuria in mice and humans lacking the intrinsic lysosomal protein SCARB2/LIMP-2  

Jia Lian Chee
Association of joint hypermobility and orthostatic intolerance with polycystic kidney disease in two unrelated individuals  

Matthew Davies
Reduced association of the metabolic regulators AMPK AND ACC1 with NKCC2 in mice fed a high fat diet  

Suet-Wan Choy
Increased plasma glucose and reduced albuminuria in AMP-activated protein kinase B1 null mice with streptozotocin-induced type 1 diabetes  

Suet-Wan Choy
Regulation of the salt co-transporter NKCC2 by AMP-ACTIVATED protein kinase (AMPK) and Acetyl CoA Carboxylase1 (ACC1)

Maree Ross-Smith
Most cases of chronic haemodialysis commencement with a catheter were not preventable: results of a four year prospective single centre audit  

Oneel Patel
Comparison of Renal Preconditioning techniques in a rat model  

Francesco Ierino
Foxp3+ T cells in peripheral blood of renal transplant recipients and clinical correlations
Speech pathology

Anita McKinstry

The validity of self-reported dysphagia in patients attending pulmonary rehabilitation programs
Poster session; Group 2 categories
2:30 PM - 3:30 PM  
Level 4 Austin Tower, Education Precinct rooms 4.4 and 4.5

Endocrinology & Metabolism

Jasmine Zhu
The direct and indirect effects of depression on glycaemic control in type 2 diabetes  
Ada Cheung
Cardiovascular risk factors and reduced bone density are highly prevalent amongst men commencing androgen deprivation therapy.
Linsey Gani
Low Testosterone as an Independent Predictor of Survival in Men with Chronic Liver Disease
Olivia Herdiman
The role of androgens in the progression of prostate cancer
Priya Sumithran
Long-term persistence of hormonal adaptations to weight loss
Emma Bannerman
The Effect of Lactation on Bone Micro-Architecture
Philip Zeglinski
Simultaneous determination of free catecholamine and metanephrine levels in plasma or urine by liquid chromatography with mass spectrometric detection.
Xiao-Fang Wang
Racial difference in bone microstructure and density at distal radius and tibia between young Chinese and Caucasian men
Tammy Pang
Investigating non-DNA binding dependent signalling pathways of the androgen receptor
Michelle Kim
Development of a questionnaire assessing self-monitoring of blood glucose behaviours and insulin self-adjustment behaviours in patients with diabetes mellitus
Michelle Kim
An investigation into the role of health behaviours and attitudes in mediating the relationship between depressive symptoms and glycaemic control in patients with diabetes on insulin
Endocrinology & Metabolism (cont’d)

Jackie How
Attenuated regional vasodilatory effects of gastrointestinal hormones in obesity prone animals: implications for obesity-related hypertension  
Patricia Russell
Identification of target genes in osteoblasts, the bone forming cells, that are regulated directly via the Androgen Receptor.  
Michele V Clarke
Delayed cortical bone growth in mice expressing EGFP-Cre fusion protein under the control of the osterix promoter.

Gastroenterology

Josephine Grace
Increased formation of splanchnic vascular angiotensin-(1-7) from angiotensin I and angiotensin II is mediated by angiotensin converting enzyme-2 in experimental cirrhosis and portal hypertension.  
Eu Jin Lim
Hepatitis C and Cyclosporine Reduce Viability and Induce Apoptosis In Liver Cells  
Jessica Howell
Different definitions of HCV rapid fibrosis post liver transplant yield insights into the fibrosis timecourse  
Jessica Howell
Toll-Like Receptor 3 and 7/8 function is impaired in HCV patients with rapid fibrosis progression post liver transplantation  
Sujie Chandran
Factors associated with recurrence of hepatocellular carcinoma post liver transplantation.  
Suong Le
Treatment of HCV in the setting of transplantation for Hepatocellular Carcinoma (HCC). A missed opportunity?  
Chandran Sujie
Risk stratification of upper GI bleeding with an oesophageal pillcam.  
Chandran S
Incidental colonic uptake on PET-CT and endoscopic correlation, the Austin experience.  
Rohit Sawhney
Changes in Toll-like receptor 2 expression on peripheral immune cells in cirrhosis  
He Liu
Role of P21-activated kinase 1 in proliferation of Colorectal Cancer cells in Vitro and in Vivo
Gastroenterology (cont’d)

Kathryn Marshall
Progastrin derived peptides are biologically active in vitro and in vivo.

Suzana Kovac
Gastrin increases its own expression through proximal DNA elements.

Suzana Kovac
Zinc increases the expression of gastrin in vitro.

Kai Yan Mak
Production of liver-specific adeno-associated virus carrying angiotensin converting enzyme (ACE2) for experimental gene therapy in liver fibrosis.

Christopher Leung
Is our diet ageing us? How advanced glycation endproducts (AGES) worsen fatty liver disease.

Christopher Leung
To TOE or not to TOE? That is the question in cirrhotic patients with varices.

Christopher Leung
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ABSTRACTS

CONTINUOUS NON-INVASIVE PERIOPERATIVE MONITORING OF CARDIAC OUTPUT BY PULMONARY CAPNOTRACKING

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Introduction: A number of technologies are available for minimally-invasive cardiac output measurement in patients during surgery but remain little used. A novel system has been developed based on CO2 elimination (VCO2) by the lungs for use in ventilated patients, which can be fully integrated into a modern anesthesia/monitoring platform, and provides automated, handsfree continuous breath-by-breath cardiac output monitoring. Methods: A prototype measurement system was constructed to measure VCO2 and end-tidal PCO2 with each breath. A baseline measurement of non-shunt cardiac output was made during a brief change in ventilator rate, according to the differential CO2 approach. Continuous breath-by-breath monitoring of cardiac output was then performed from measurement of VCO2, using a derivation of the Fick equation applied to pulmonary CO2 elimination. Automated recalibration was done periodically or on command by the anesthesiologist. Data was processed and cardiac output displayed in real time. Measurements were compared with simultaneous measurements by bolus thermodilution in 77 patients undergoing cardiac surgery or liver transplantation. Results: Overall mean bias [sd] for agreement in cardiac output measurement (capnotracking – thermodilution) was – 0.1 [1.2] L/min, r = 0.92. Concordance in measurement of changes in cardiac output was 90.4%. The method followed sudden changes in cardiac output due to arrhythmias and run onto cardiopulmonary bypass in real time. Conclusions: The accuracy and precision were comparable to other more invasive clinical techniques. The method is seamless and automated and has potential for continuous, cardiac output monitoring in ventilated patients during anesthesia and critical care.

INVESTIGATION OF VENTILATION-PERFUSION SCATTER IN THE LUNG DURING ANAESTHESIA USING THE MIGET

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Induction of general anaesthesia produces deterioration in ventilation-perfusion (V/Q) matching in the lung, contributing to the inefficiency of gas exchange seen in anaesthetized patients. The MIGET (Multiple Inert Gas Elimination Technique) is the gold standard method for characterization of V/Q distributions. It involves intravenous infusion of a trace mixture of 6 inert volatile substances in solution. Trace partial pressures of the six gases in arterial blood and expired gas are measured and the retention (Pa/Pv) and excretion (PE'/Pv) of the gases allows computation of 50 compartment distributions of V/Q in the lung. We validated a system for performance of the MIGET using a refitted HP/Agilent 5793/6890N GCMS. Linearity of response for the six gases at typical trace concentrations was confirmed by 250X serial dilution. An adaptation of the MIGET for use in intubated patients was developed and tested. Patients were anaesthetised with TIVA propofol. Cardiac output was measured using a FloTrac, and minute ventilation by a specially designed system using an extractable flow marker gas. Paired arterial and end-tidal gas samples were collected after 10 minutes of stable haemodynamics and ventilation. Blood samples were processed for GCMS analysis by the headspace equilibration method in gas-tight glass syringes. The system will be used to enable further studies into the effect of V/Q scatter on gas exchange using a physiological model employing a double lumen endotracheal tube in patients undergoing thoracic surgery. Data from this study will be presented.

(1) Roca J, Wagner PD. Contribution of multiple inert gas elimination technique to pulmonary medicine. 1. Principles and information content of the multiple inert gas elimination technique. Thorax 1994 49
THE PRESENCE OF RETINAL MICROVASCULAR DYSFUNCTION IS A PREDICTOR OF UNDERLYING CORONARY ARTERY DISEASE

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Introduction: Endothelial dysfunction is a key early feature of systemic atherosclerosis and identification may lead to targeted screening and increased preventive therapies. Retinal microvascular dilatation in response to flicker light, a nitric oxide-dependent phenomenon, can be assessed non-invasively. We sought to determine if retinal microvascular function is impaired in patients with coronary artery disease (CAD).

Methods: Stable patients with or without CAD were recruited (n=194). CAD was defined as chest pain with a positive functional study and/or a coronary angiographic stenosis of >50%. Retinal vascular reactivity in response to diffuse luminance flicker light was measured using the Digital Vessel Analyzer (IMEDOS, Germany) after pupil dilatation. Retinal arteriolar dilatation (RAD) is expressed as percentage diameter increase over baseline. An average of both eyes per patient was recorded.

Results: Subjects with CAD (n=75) were older (63±9 versus 55±12 years; P<0.01), more likely to be male (83% versus 55%; P<0.01) and have dyslipidaemia (96% versus 74%; P<0.01) than subjects without CAD. RAD was attenuated in patients with CAD (1.5 ± 0.2% versus 2.4 ± 0.2%, mean ±SEM; P=0.003). Each 1% decrease in RAD was associated with a 33 % higher risk of having CAD after adjustment for age, gender, body-mass index, smoking, hypertension and dyslipidaemia (OR 1.33, 95% CI 1.05 – 1.67 ).

Conclusion: RAD in response to flicker light is attenuated in stable CAD patients. The capacity of retinal arterioles to dilate is an independent predictor of the presence of CAD. These findings suggest that endothelial dysfunction in the retinal microcirculation may be a marker for underlying CAD.

EFFECT OF VENOUS PRESSURE ON FRACTIONAL FLOW RESERVE AND INDEX OF MICROCIRCULATORY RESISTANCE IN PATIENTS WITH STABLE CHEST PAIN SYNDROMES

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Purpose: Fractional flow reserve (FFR) is the ratio of distal to proximal coronary pressure (Pd/Pa ) during maximal hyperaemia. Physiologic significance of a coronary stenosis is determined if FFR ≤0.80. The index of microcirculatory resistance (IMR) is used in research studies and is calculated as Pd x hyperaemic mean transit time (Tmn). Higher IMR values are a marker of coronary microcirculatory dysfunction. For simplicity, calculation of FFR and IMR assumes a negligible venous pressure (Pv). We hypothesised that accounting for venous pressure is important in determining lesion significance and microvascular function.

Methods: Thirty two patients (10 females; age 65 ±9 years), with stable chest pain syndromes undergoing coronary angiography were recruited. Physiologic studies were performed in 32 coronary arteries with a pressure guidewire. Maximal coronary hyperaemia was induced by femoral intravenous adenosine infusion at 140 µg/kg/minute. IMR was calculated after the rapid guide catheter injection of a 3mL saline bolus during hyperaemia. Pv was measured from the femoral sheath and FFR and IMR was recalculated (FFR = [Pd- Pv]/[Pa- Pv] and IMR = [Pd- Pv] x Tmn ).

Results: Baseline and hyperaemic Pv were similar (mean ± SD; 13.8 ± 6.0 vs 13.6 ± 4.9 mmHg; p = 0.89). FFR was lower when Pv was included (0.83 vs 0.80; p <0.01; n=32). In six patients with borderline FFR between 0.80 and 0.85, accounting for venous pressure resulted in reclassification of five lesions as significant (FFR ≤0.80). IMR was also significantly lower when Pv was included (16 vs 12 units; p <0.01).

Conclusion: These data suggest that Pv has a clinically important effect on FFR and IMR values, and perhaps it should be taken into account in clinical and research studies to accurately determine the fractional flow reserve and microcirculatory resistance.
GLOBAL LONGITUDINAL STRAIN IS A STRONG INDEPENDENT PREDICTOR OF ALL-CAUSE MORTALITY IN PATIENTS WITH AORTIC STENOSIS

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Background: Global longitudinal strain (GLS), measured with speckle tracking echocardiography, is a sensitive marker of LV systolic function, however its prognostic capacity in patients with aortic stenosis (AS) is uncertain. We hypothesised that in patients with AS, GLS would predict: 1) All-cause mortality and 2) Major adverse cardiac events (MACE: death or hospitalisation due to cardiac causes).

Methods: Subjects with AS (n=146) and controls (n=10) underwent baseline echocardiography to assess AS severity and GLS. GLS was graded as: normal function (GLS<-20%), mild dysfunction (GLS: -15 to -19.9%), moderate dysfunction (GLS: -10 to -14.9%) and severe dysfunction (GLS> -10%). Baseline demographics, symptom severity class (composite of angina/dyspnoea/syncope) and comorbidities were recorded. Outcomes were identified via hospital record review.

Results: The age (mean ± SD) of subjects was 75 ± 11, 62% were male. Baseline aortic valve area (AVA) was 1.0 ± 0.4cm² and LVEF was 59 ± 11%. Subjects with AS had lower GLS (-15 ± 4%) than controls (-21 ± 2%) (p<0.001) and GLS was associated with symptom severity (p<0.001). During a mean follow-up of 1.4 ± 0.4 years, there were 14 deaths and 90 MACE. Unadjusted hazard ratios for GLS were: all-cause mortality (HR 6.4 (per grade) (2.8 -14.3), p<0.001) and MACE (HR 1.5 (per grade) (1.2 -2.0), p=0.002). With multivariate analysis, GLS (HR 6.2 (2.1 -17.9), p=0.001) was a stronger predictor of all-cause mortality than AVA (per cm²) (HR 0.19, p=0.053), symptom class (HR 1.69, p=0.07) and LVEF (1.01, p=0.84).

Conclusion: GLS independently predicts all-cause mortality in AS and its incorporation into risk stratification models may enable better identification of the optimal timing for aortic valve replacement.

UTILITY OF CARDIAC MAGNETIC RESONANCE IMAGING FOR THE ASSESSMENT OF PROSTHETIC AORTIC VALVES

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Background: Cardiac magnetic resonance imaging (CMR) allows assessment of valve morphology and haemodynamics; however the utility of CMR in the assessment of prosthetic aortic valves is unknown. We assessed the correlation between trans-thoracic echocardiography (TTE) and CMR techniques for the measurement of peak aortic valve (AV) velocity and aortic valve area (AVA).

Methods: 28 patients with AV prosthesis (n=21 bioprosthesis, n=7 mechanical prosthesis) underwent same day assessment with TTE and CMR. TTE measurements were peak AV velocity (TTE-Vmax) and AVA by Continuity equation (TTE-AVA). With CMR, peak velocity was measured with velocity-encoded phase contrast imaging (CMR-Vmax) and AVA via Continuity equation (CMR-AVAcont) and planimetry (CMR-AVAplan; bioprosthesis only). CMR assessments were performed blind to the TTE results.

Results: The age (mean ± SD) of subjects was 68 ± 11 years, 68% were male and BMI was 30 ± 5 kg/m². There were good correlations between TTE-Vmax and CMR-Vmax (r=0.57, p=0.002) and for TTE-AVA and CMR-AVAcont (r=0.59, p=0.003). There was no correlation between the TTE-AVA and CMR-AVAplan (r=0.24, p=0.33).

Conclusions: CMR provides a satisfactory, non-invasive alternative for the assessment of prosthetic aortic valves when the TTE is not diagnostic; however planimetry of aortic valve prostheses is unreliable due to valve-related artefact.
ASSOCIATION OF ACE2 GENETIC VARIANTS WITH BLOOD PRESSURE, LEFT VENTRICULAR MASS AND CARDIAC FUNCTION IN CAUCASIANS WITH TYPE 2 DIABETES.

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Aim: Cardiovascular disease is common in diabetes, and is associated with activation of the renin-angiotensin system (RAS). Angiotensin converting enzyme (ACE) 2 is a recently described member of the RAS, and this study investigated if ACE2 polymorphisms are associated with hypertension, left ventricular (LV) mass and cardiac function in type 2 diabetes. Methods: Variants in ACE2 (rs1978124, rs2074192, rs4240157, rs4646156, rs4646188) were examined in 503 Caucasian subjects with type 2 diabetes. As ACE2 is located on the X chromosome, analyses were performed separately for men and women. Hypertension was defined by a history of hypertension, and/or antihypertensive medications or blood pressure (BP) >130/80 mmHg. LV mass and systolic function (ejection fraction) were assessed by transthoracic echocardiography. Results: In men, hypertension was more prevalent with the ACE2 rs2074192 C allele (p = 0.023), rs4240157 G allele (p = 0.016) and rs4646188 T allele (p = 0.006). In men, the rs1978124 A allele was associated with a significantly lower ejection fraction compared to the G allele [62.3 ± 13.3 vs. 67.2 ± 10.9 %, p = 0.002]. This association remained significant after covariate adjustment for age, BMI, hypertension, anti-hypertensive treatment and BP. In women, the prevalence of hypertension was higher (p = 0.009) with the rs4240157 G allele, and the rs1978124 A allele was associated with significantly higher LV mass (p = 0.008). Conclusion: In Caucasians with type 2 diabetes, genetic variation in ACE2 is associated with hypertension and reduced systolic function in men, and hypertension and increased LV mass in women.

LEFT VENTRICULAR HYPERTROPHY IN TYPE 2 DIABETES; EFFECT OF INDEXING TO HEIGHT VERSUS BODY SURFACE AREA ON PREVALENCE AND CARDIOVASCULAR EVENTS.

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Aim: Left ventricular hypertrophy (LVH) is associated with major adverse cardiovascular events (MACE). This study investigated if normalising left ventricular (LV) mass to body surface area (BSA) or to height would affect the prevalence of LVH and the risk of MACE in type 2 diabetes mellitus (T2DM). Methods: 1072 subjects with T2DM were recruited prospectively. An echocardiogram was performed and subjects were followed for a median of 4.0y. LVH was defined as either LV mass indexed to BSA (males > 115g/m², females > 95g/m²) or indexed to height (males > 49g/m², females > 45g/m²). MACE was defined as all cause mortality, stroke, heart failure admission, acute coronary syndrome and coronary and peripheral vessel revascularisation. Results: Overall, 35% of subjects were overweight (body mass index (BMI) ≥ 25 and < 30kg/m²) and 49% were obese (BMI ≥ 30kg/m²). The prevalence of LVH-BSA was 32% and LVH-height was 52%. In normal weight subjects (BMI < 25kg/m²), the prevalence of LVH-BSA and LVH-height was similar. However, LVH was significantly higher when indexed to height in the overweight and obese subjects (P < 0.01). During follow up, 265 MACE occurred. The hazard ratio for MACE (adjusted for age, gender, cardiovascular risk factors, T2DM duration, macro- and micro-vascular complications) was similar for LVH-BSA (1.57 [95% CI 1.19-2.07], P=0.002) and LVH-height (1.58 [1.17-2.11], P=0.003). The adjusted population-attributable risk for LVH-height was 1.5 fold greater than for LVH-BSA in the whole cohort. Conclusion: It is more appropriate to index LV mass to height to define LVH in a T2DM cohort with high rates of obesity.
EVALUATION OF RIGHT VENTRICULAR VOLUME AND SYSTOLIC FUNCTION - A COMPARISON OF 2 AND 3-DIMENSIONAL ECHOCARDIOGRAPHY WITH CARDIAC MAGNETIC RESONANCE

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Background: Cardiac magnetic resonance (CMR) is the gold standard for non-invasive assessment of right ventricular (RV) size and function, but is limited in availability. Real time 3-dimensional echocardiography (RT3DE) is an emerging technology. We compared 2D and 3D echo with CMR for RV assessment.

Method: Patients referred for CMR underwent echocardiography on the same day. We measured RV volumes and ejection fraction (EF) on both RT3DE and CMR; RV area (RVA), fractional area change (FAC) and diastolic right ventricular internal diameter (RVID) on 2D.

Results: 45 patients were recruited (mean age 45; 60% male). 3D image analysis was performed on 34 (suboptimal image quality in 11). The Correlation between RT3DE and CMR RVEF was significant (r=0.59, p<0.001), RT3DE RV end diastolic and end systolic volumes (RVEDV and RVESV) correlated significantly with CMR (RVEDV r=0.70, p<0.001; RVESV r=0.84, p<0.001). 2D measurements were suitable for analysis in 39 patients. 2D and CMR measurements correlated strongly: RVA vs CMR volumes (RVEDV r=0.84, p<0.001; RVESV r=0.86, p<0.001), RVFAC vs CMR RVEF (r=0.35, p=0.03). RVID had strong correlations with all other measurements for RV size (CMR RVEDV r=0.78, p<0.001; 3D RVEDV r=0.76, p<0.001; 2D RV area r=0.76, p<0.001).

Conclusion: RT3DE is comparable to CMR for RV volume and EF assessment. 2D RV area and RVID correlates with CMR RV volume, which may be helpful in patients with poor RT3DE image quality.

LIPID EXPOSURE ENHANCES ARTERIAL GRAFT PATENCY VIA THE NATIVE VESSEL PATHWAY: AN ILLUSTRATION OF THE COMPETITIVE FLOW PHENOMENON AFTER CORONARY SURGERY

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OBJECTIVES: Hypercholesterolemia is a well-known risk factor for coronary artery disease. We sought to explore the long-term effects of lipid exposure on bypassed native vessels and their grafts in patients after coronary surgery.

METHODS: CABG patients from a radial artery trial were retrospectively reviewed for lipid study and angiography results. Using all available post-operative lipid assays from pathology laboratories, we calculated mean-annualised lipid exposures for total cholesterol, HDL, LDL and triglycerides. Disease progression between pre-operative and post-operative angiograms was recorded for each major native vessel. Graft performance was reported as failed or patent. We examined for correlations between lipid exposure, native vessel disease progression and graft patency.

RESULTS: We analysed 3801 native vessels amongst 405 patients a mean of 6.2±3.1 years after surgery. Overall, increased LDL and decreased HDL correlated with more severe disease progression (p=0.004, p=0.001). With arterial-grafted native vessels (n=800), elevated LDL/HDL and Total-C/HDL were both associated with progression of stenosis (p=0.009, p=0.009). Progressive stenosis in turn correlated with superior arterial graft performance (p<0.001). For direct relationships between lipids and arterial grafts, increased total cholesterol and LDL were both favourably correlated with reduced risk of graft failure (p=0.047, p=0.045).

CONCLUSION: Grafted native vessels develop progressive disease in response to elevated lipids, analogous to untreated coronary disease. This increasing stenosis appears to benefit arterial graft performance, possibly due to reduced competitive flow, thereby counter-intuitively allowing increased lipids to be protective of arterial grafts. The presumed detrimental effects of lipids in the context of bypass surgery should not be interpreted independently of the competitive flow phenomenon.
ELECTRICAL CHARACTERISTICS OF MULTIPOLAR LEFT VENTRICULAR PACING LEADS

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Background: Multipolar left ventricular pacing leads used with cardiac resynchronization therapy (CRT) may reduce complications of phrenic nerve stimulation (PNS) and high pacing thresholds (PT). The additional pacing vectors of multipolar leads may improve the optimization of electrical parameters.

Methods: 10 Patients undergoing CRT were implanted with a Quartet lead, (LV4) and a Promote Quadra St. Jude Medical CRTD enabling sensing and pacing in 10 bipolar configurations. In each of the pacing configurations, the PT and PNS were measured. The right to left ventricular electrogram (EGM) timing was measured in intrinsic rhythm and during right and left ventricular pacing.

Results: 10 patients received an LV4 lead; a vertical lateral wall placement was achieved in all. In each patient significant differences in EGM timing and thresholds were seen across the pacing configurations. All patients had at least one electrode pair with a PT<1.5mv, and PNS at least 2.5 times greater than PT. In 3 patients the distal pair could not be used due to high PT in 1 patient and due to PNS in 2 patients. In individual patients, the RV to LV EGM timings differed by as much as 60 (18 – 60) ms across the lateral wall bipolar electrode pairs.

Conclusion: The different pacing configurations in LV4 leads provide significant differences in PT, PNS and EGM timing. This may reduce common LV pacing lead complications and enhance device optimization.
SUPER-RESPONDERS TO CARDIAC RESYNCHRONISATION THERAPY (CRT)
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Background: A proportion of patients implanted with CRT experience a normalization of left ventricular systolic function and resolution of heart failure symptoms. The aim of this study was to identify the predictors of this super-response (SR) to CRT.

Methods: Patients implanted with a CRT device were prospectively recruited. Clinical and device follow up was conducted at 3 monthly intervals. SR was defined by normalization of LVEF (>50%), normalization or >30% reduction in LVESV or a decrease in New York heart Association (NYHA) functional class >1 symptoms. The clinical, echocardiographic and device electrical characteristics of SR were compared to responders and non-responders (NR).

Results: 453 patients were enrolled. By our definition there were 35 (8%) SR, with an overall response rate of 82% and NR 18%.

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>Responders</th>
<th>P value SR vs R</th>
<th>NR</th>
<th>P value SR vs NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65</td>
<td>67</td>
<td>NS</td>
<td>68</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>87%</td>
<td>84%</td>
<td>NS</td>
<td>81%</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>58%</td>
<td>66%</td>
<td>NS</td>
<td>73%</td>
<td>P=0.06</td>
</tr>
<tr>
<td>AF</td>
<td>21%</td>
<td>23%</td>
<td>NS</td>
<td>25%</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF</td>
<td>26%</td>
<td>28%</td>
<td>NS</td>
<td>28%</td>
<td>NS</td>
</tr>
<tr>
<td>Dyssynchrony</td>
<td>53</td>
<td>49</td>
<td>NS</td>
<td>44</td>
<td>P=0.04</td>
</tr>
<tr>
<td>LBBB</td>
<td>93%</td>
<td>91%</td>
<td>NS</td>
<td>88%</td>
<td>NS</td>
</tr>
<tr>
<td>EGM difference</td>
<td>115ms</td>
<td>108ms</td>
<td>NS</td>
<td>86ms</td>
<td>P=0.02</td>
</tr>
</tbody>
</table>

Pre-procedural demographic data including duration of heart failure symptoms did not predict super-response to CRT. 71% of super-responders self reported an immediate improvement in symptoms following CRT.

Conclusions: Using resolution of heart failure as our definition we identified a SR rate of 8%. We did not identify any predictors of SR compared with normal responders, but demonstrated that increased dyssynchrony and the ability to implant leads in areas of increased dyssynchrony predicted SR compared with NR.
5 YEAR EXPERIENCE WITH CRT IN A MULTIDISCIPLINARY SERVICE.
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Objective: To determine the outcome of patients receiving cardiac resynchronization therapy (CRT) in a high volume service incorporating electrophysiologists, echo optimization and heart failure specialists.

Methods: All patients undergoing CRT implantation from 1/2006 – 6/2010 were recruited. Device and clinical follow up was conducted at 3 monthly intervals. Echocardiographic assessments of dyssynchrony were performed prior to implant and optimization post implant.

Results: 435 initial CRT implants were performed. Mean age 67 years, 83% male, 62% ischaemic aetiology. Mean QRSd 151 msec, QRSd >120msec in 93%. LBBB was present in 91% AF present pre-implant in 23%. Echocardiographic response rate to CRT was 81%, with 35 (8%) super responders. 87% of patients improved by at least 1 NYHA class. The mean EF improved from 28% to 39%. The mean LVEDD decreased from 6.7cm to 6.2cm. The mean NYHA class improved from 2.7 to 1.4. The mean dyssynchrony index improved from 48 to 30. Predictors of response to CRT were sinus rhythm at implant, higher baseline dysynchrony scores and implant EGM difference of >80 msec. Response rates improved during the period of analysis. Successful LV lead implantation at initial procedure was achieved in 99.1%. LV lead survival at latest follow was 94.1%; 11(2.5%) leads were unable to be used or required reposition due to diaphragmatic stimulation, 12 (2.7%) of leads developed elevated thresholds or displaced. Implant complication rate requiring intervention was 0.9%.

Conclusion: CRT in a high volume service can provide a high level of response with acceptable rates of complications.

SHOCK REDUCTION IN IMPLANTABLE CARDIOVERTER DEFIBRILLATORS – A LOCAL PERSPECTIVE
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Background: Shocks from automated implantable cardioverter defibrillators (ICDs) are associated with psychological and financial cost. Compelling data suggests that ICD shocks are associated with increased mortality.

Methods: Patients implanted with an ICD were prospectively recruited between 1/2005 and 6/2010. Device follow up was conducted at 3 monthly intervals. All device-delivered shocks and device treated ventricular arrhythmias (VA) were recorded and analysed. Inappropriate shocks were defined as any shock delivered in the absence of a sustained VA. The use of long detects, ATP, lead integrity alert and home monitoring was encouraged in all patients.

Results: 1076 patients with 4056 patient-years of follow up were enrolled. 4.1% of patients per year experienced a shock. Of these 411 shocks in 106 patients were appropriate shocks (76%) and 143 shocks in 59 patients were inappropriate shocks (24%). Inappropriate shocks were due to atrial fibrillation in 55%, supraventricular tachycardia / sinus tachycardia in 12% and noise / over-sensing in 33%. During the study period there was a significant increase in all treated VA but a significant reduction in both inappropriate and appropriate shocks. The ratio of appropriate to inappropriate shocks did not change significantly. The predictors of any shock were secondary prevention and symptomatic heart failure. The only predictor of inappropriate shocks was implant for primary electrical disease.

Conclusions: Compared to international registries, our local experience suggests that shock reduction can be achieved with attention to device programming and patient follow up.
CHARACTERISATION OF NATIVE VESSELS DISEASE IN CORONARY ARTERY BYPASS GRAFT PATIENTS

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OBJECTIVE: The performance of grafted conduits after coronary artery bypass grafting (CABG) is well characterised. However, the behaviour of native coronary vessels in the long-term after bypass surgery remains unclear. METHODS: Amongst 619 CABG patients from a radial artery trial, 405 underwent follow-up angiography a mean of 6.2±0.1 years after surgery. Percent diameter stenosis in each major native vessel was independently reported by 3 cardiac specialists and graded from 0-4 based upon clinical significance. Change from pre-operative grade was analysed both by prevalence across the major coronary circulations and by graft presence, type and patency. RESULTS: 3801 native vessels were analysed, 1242 of which were grafted. Overall, disease progression was more prevalent within the right circulation (p<0.001), whilst prevalence of disease regression was greater in the left (p<0.001). Grafting a native vessel was associated with greater disease progression (p<0.001). Progression of disease was also correlated with a decreased risk of graft failure (p<0.001), irrespective of graft type. Correspondingly, disease regression trended towards an increase in risk of arterial graft failure (p=0.066). CONCLUSION: Key characteristics of the right circulation appear to promote disease progression compared to the left. Bypassing a native vessel appears to accelerate its disease progression, which in turn influences the performance of the graft, whether arterial or venous. Surprisingly, disease regression was dependent on graft type; disease regression correlated with greater arterial graft failure. These results imply the effects of competitive flow with regard to both progression and regression of disease, as well as in both arterial and venous grafts.

TRICUSPID REGURGITATION IS AN INDEPENDENT PREDICTOR OF MORTALITY IN ACUTE PULMONARY EMBOLISM

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\textsuperscript{2}Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia

Background: Right ventricular (RV) dysfunction on echocardiography is an independent predictor of early death in pulmonary embolism (PE). However, assessment of RV function may be inaccurate using 2-D echocardiography. We analysed whether severity of tricuspid regurgitation (TR), a more objective echocardiographic feature of RV dilatation and dysfunction, is associated with mortality in patients with PE.

Methods: Consecutive patients with confirmed PE on CTPA or V/Q scan managed at Austin Health between January 2007 and February 2011 who had transthoracic echocardiography were retrospectively enrolled. Echocardiographic characteristics recorded included RV dilatation, RV hypokinesis, degree of TR, pulmonary artery systolic pressure (PASp) and inferior vena cava (IVC) dilatation. Primary outcome was all cause mortality. Cox regression analyses were performed to identify predictors of mortality.

Results: 115 patients were enrolled (54% female), mean age 60±16 years. Mean follow-up was 1.6 ± 1.2 years, during which 15 patients (13%) died. On echocardiography, 51% had RV dilatation, 49% had RV hypokinesis, 14% had moderate or severe TR and 52% had IVC dilatation. Mean PASp was 39 ± 16 mmHg (+ RAp). In multivariable analysis, TR severity (OR 2.44, 95% CI 1.50-3.96; p<0.001) and PASp (OR 1.03, 95% CI 1.01-1.06; p=0.017) were independent predictors of mortality.

Conclusion: TR severity and PASp are independent predictors of mortality in acute PE. This study confirms the value of transthoracic echocardiography for risk stratification and assessment of prognosis in these patients.
Background: Cardiac rhythm monitoring is used for early detection of arrhythmias in a variety of patients, but the frequency of arrhythmia detection may be low. We sought to determine arrhythmia frequency in patients on cardiac telemetry, and whether patient management was altered. Methods: 512 consecutive patients admitted to telemetry in a tertiary hospital were prospectively recruited over a 4-month period. Elective cardiac procedural patients were excluded. Significant arrhythmias included supraventricular tachycardias (SVT), ventricular tachycardia (VT) or fibrillation (VF), sinus node or atrioventricular conduction abnormalities. Outcomes included significant new arrhythmias, change in management, and all-cause mortality. Results: 422 (82.4%) patients had no arrhythmias detected. Significant arrhythmias were detected in 90 patients (17.6%): VT 3(3%), NSVT 45(50%), complete heart block 1(1%), second degree heart block 3(3%), pauses >3.0s 9(10%), junctional bradycardia 5(5%), and SVT 49(54%). Change in management occurred in 65 patients (12.7%): cardiac life support 3(5%), permanent pacemaker 11(17%), implantable cardioverter defibrillator 1(1%), temporary pacing wire 1(1%), electrophysiology study 1(1%), intravenous medications 14(22%), oral medication change 49(75%). There were 29 medical emergency calls during telemetry, 10 arrhythmia-related. One patient (0.2%) died on telemetry from a non-cardiac cause.

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arrhythmia (n = 90)</th>
<th>No Arrhythmia (n = 422)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age +/- SD (years)</td>
<td>69.5 +/- 12.3</td>
<td>66.4 +/- 14.6</td>
<td>0.05</td>
</tr>
<tr>
<td>% Male (n)</td>
<td>68.9% (62)</td>
<td>66.8% (282)</td>
<td>0.93</td>
</tr>
<tr>
<td>% with ACS (n)</td>
<td>28.9% (26)</td>
<td>20.4% (86)</td>
<td>0.03</td>
</tr>
<tr>
<td>% pre-existing arrhythmia (n)</td>
<td>28.9% (26)</td>
<td>28.4% (120)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Conclusion: Our patient cohort revealed a small group of patients with new arrhythmias detected on cardiac telemetry, with subsequent changes in management. These patients were older and more frequently had ACS. Further refinement of admitting protocols are required to facilitate optimal allocation of this limited resource.
IS OBESITY A RISK FACTOR FOR ADVERSE OUTCOME FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)?


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2 Department of Medicine, University of Melbourne
3 Monash Centre of Cardiovascular Research & Education in Therapeutics, Monash University
4 Department of Cardiothoracic Surgery, St Vincent's Hospital
5 Department of Cardiothoracic Surgery, Monash Medical Centre
6 Department of Cardiology, Royal Melbourne Hospital
7 Department of Cardiology, The Alfred Hospital

Aim: Paradoxically, overweight and obese patients have been shown to have improved outcomes compared with normal weight individuals following percutaneous coronary intervention. We sought to determine if obesity is a risk factor for adverse outcome following CABG or whether a similar "obesity paradox" is evident.

Methods: We evaluated data from 19,867 patients undergoing isolated CABG between 2001 and 2010, enrolled in the Australasian Society of Cardiac and Thoracic Surgeons registry. Patients were classified as underweight, normal, overweight, mildly obese and very obese; body-mass index <20, 20–25, 25.1–30, 30.1–35 and >35kg/m². We compared in-hospital, 30-day and longer-term (mean 3.7 years) outcomes.

Results: Obese patients were younger with a higher prevalence of traditional cardiovascular risk factors and prior myocardial infarction (MI). Non-obese patients were more likely to present with peripheral vascular disease, cerebrovascular disease, recent MI, heart failure and cardiogenic shock. Obese patients had longer cardiopulmonary bypass times but were less likely to require mechanical circulatory support, blood transfusions or reoperation. Deep sternal wound infection was highest in very obese patients compared with normal patients (1.7% vs. 0.5%, p <0.001). Mortality rates are shown in the table below.

<table>
<thead>
<tr>
<th>BMI Category kg/m² (n)</th>
<th>&lt;20 (378)</th>
<th>20–25 (4539)</th>
<th>25.1-30 (8666)</th>
<th>30.1–35 (4907)</th>
<th>&gt;35 (1377)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality (%)</td>
<td>4.8</td>
<td>2.2</td>
<td>1.2</td>
<td>1.3</td>
<td>1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-term mortality (%)</td>
<td>28.7</td>
<td>15.1</td>
<td>10.3</td>
<td>10.2</td>
<td>12.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Following multivariate analysis, BMI>25.1kg/m² conferred a protective effect for 30-day and long-term mortality (HR 0.60, 95%CI 0.46-0.77, p≤0.001).

Conclusions: Compared with underweight and normal-weight individuals, obese patients had lower in-hospital, 30-day and long-term mortality. Although obese patients must be encouraged to lose weight for its long-term benefits, surgery should not be denied for any perceived increased risk of mortality.
ANGIOTENSIN CONVERTING ENZYME 2 (ACE2): A NOVEL MARKER OF CORONARY ARTERY DISEASE IN MAN
Freeman M1,2, Patel SK1, Lancefield T1,2, Velkoska E1, Griggs K1, Dean RG1, Al-Fiadh A1,2, Horrigan M2, Farouque HMO1,2, Burrell LM1,2.
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2 Department of Cardiology, Austin Health, Melbourne, Australia.

Purpose: Expression of ACE2, a newly discovered member of the renin angiotensin system, is increased in the ischemic heart and atherosclerotic plaques in experimental models. The effect of CAD on circulating ACE2 levels in man is unknown. We hypothesised that ACE2 levels may increase in patients with CAD.

Methods: 274 patients requiring coronary angiography for suspected CAD were recruited between 2008 and 2011. Blood was taken from the femoral artery, coronary artery ostium and the coronary sinus. Plasma ACE2 activity was measured using a quenched fluorescent substrate, and compared in those with angiographically normal coronary arteries (NCA, defined as < 50% stenosis), and significant CAD (> 50% stenosis in ≥ 1 major epicardial vessel).

Results: The mean ± SD age was 65 ± 10 years, body mass index 30 ± 6 kg/m² and 65% were male. ACE2 activity was not significantly different between the 3 sites (P = 0.26). There was a significant main effect with ACE2 activity and CAD (P <0.0001). ACE2 activity (geometric mean) was higher in CAD compared to NCA at the femoral artery (25.8 vs. 16.9 pmol/min/ml, P = 0.003), coronary artery (22.5 vs. 14.0 pmol/min/ml, P = 0.002), and coronary sinus (23.0 vs 14.7 pmol/min/ml, P = 0.006). These differences remained significant after adjusting for age and gender.

Conclusion: Circulating ACE2 activity reflects the burden of coronary atherosclerosis with increased levels observed in those with angiographically proven CAD.

DOES THE ADDITION OF A RADIAL ARTERY GRAFT IMPROVE SURVIVAL AFTER HIGHER RISK CORONARY ARTERY BYPASS GRAFTING? A PROPENSITY-SCORE ANALYSIS OF A MULTICENTRE DATABASE.

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Background: Use of the radial artery as a second arterial graft during coronary surgery has become popular due to high patency and encouraging clinical outcomes. It is unclear whether higher risk patients derive such benefits.

Methods: We analysed a total of 11,388 patients undergoing isolated multi-vessel coronary surgery from 2001-2009. We identified a higher risk subgroup (n=3,149) according to emergent status, coronary instability, low ejection fraction, aortic balloon counterpulsation and anticoagulant status. Among these, 2,231 (71%) received at least 1 radial graft in addition to a left internal thoracic artery (LITA). The remaining 918 (29%) received LITA and veins only.

Results: Higher risk patients who did not receive a radial were more likely have poor left ventricular function, left main stenosis and be of emergent status. These patients experienced higher unadjusted 30-day mortality (radial: 2.2% vs. veins: 7.1%, p<0.0001) and lower 7-year survival (p<0.0001). Subsequently, 548 patients in the radial group were propensity-matched to 548 receiving LITA and veins. At 30 days, there were comparable rates of mortality (2% vs. 3%, p=0.19) and mortality/any morbidity (30% vs. 32%, p=0.33). At 7 years, survival between radial and vein groups was similar (79±2.5% vs. 80±2.5%, p=0.74). Propensity-adjusted regression did not show radial artery to be protective from 30-day or mid-term mortality.

Conclusion: This multicentre analysis suggests that patients with the greatest coronary instability, urgency of surgery, or impairment of ventricular function are not disadvantaged in the early and mid-term by use of a single radial arterial graft in addition to a LITA.
IV DROPERIDOL OR OLANZAPINE AS ADJUNCTS TO MIDAZOLAM FOR THE ACUTELY AGITATED PATIENT: A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL TRIAL

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⁴Emergency, Royal Melbourne Hospital, Parkville, VIC, Australia
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Objective: To determine if IV droperidol or olanzapine, as adjuncts to midazolam administration, improve sedation quality for the acutely agitated ED patient

Methods: We undertook a randomised, double-blind, placebo-controlled, double-dummy, clinical trial in three EDs (August 2009 to March 2011). Adult patients requiring IV drug sedation for acute agitation were enrolled. Each was randomized to receive an IV bolus of either saline (control), droperidol (5mg) or olanzapine (5mg). This bolus was immediately followed by an IV midazolam bolus (2.5-5mg) then additional boluses until sedation to a pre-determined endpoint was achieved. The primary outcome was time to sedation. Secondary outcomes were the need for ‘rescue’ sedation and adverse events.

Results: 336 patients were enrolled. The baseline characteristics of the groups did not differ (p>0.05). However, the median (IQR) times to sedation (min) differed significantly (p<0.001): control group 10 (4-25), droperidol 6 (3-10), olanzapine 5 (3-10). At any time point, patients in the droperidol and olanzapine groups were ~1.6 times more likely to be sedated compared to controls: droperidol and olanzapine group hazard ratios (95%CI) were 1.58 (1.21-2.06) and 1.64 (1.25-2.15), respectively, (p=0.001). The droperidol and olanzapine groups required less rescue sedation and alternative drug use at any time after initial sedation had been achieved (p<0.05). The group adverse event profiles and lengths of stay did not differ (p=0.21 and 0.32, respectively).

Conclusions: Droperidol or olanzapine administration, as adjuncts to midazolam, is safe and significantly improves sedation quality. These findings will inform best-practice for sedation of the acutely agitated ED patient.

MEETING A SIMPLE CLINICAL TARGET RESULTS IN A HIGH LEVEL OF PATIENT SATISFACTION WITH THEIR PAIN MANAGEMENT

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²Medicine, University of Melbourne, Parkville, VIC, Australia
³Pharmacy, Austin Health, Heidelberg, VIC, Australia

Objective: To confirm that the provision of ‘adequate analgesia’ (defined as a decrease in pain score to <4 and a decrease from the triage pain score of ≥2 [scale 0-10]) is significantly associated with a high level of patient satisfaction with their pain management.

Methods: We undertook a prospective cohort study in a large academic emergency department (ED). Consecutive adult patients, with triage pain scores ≥ 4, were enrolled. Variables examined included demographics, presenting complaint, pain score every 30 minutes, nurse-initiated analgesia provision, analgesia administered, time to analgesia, specific communication regarding pain, and whether ‘adequate analgesia’ (as defined) was provided. The primary endpoint, determined by a blinded investigator 48 hours post-discharge, was the level of patient satisfaction with their pain management (6-point scale: very unsatisfied-very satisfied). Multivariate (logistic regression) analyses were undertaken.

Results: 476 patients were enrolled: mean age 43.6 ± 17.2 years, 237 (49.8%) males. 190 (39.9%, 95% CI 35.5-44.5 ) patients were ‘very satisfied’ with their pain management and 207 (43.5%, 95% CI 39.0-48.1 ) patients were provided with ‘adequate analgesia’. Three variables were significantly associated with being very satisfied: the provision of ‘adequate analgesia’ (OR 7.8, 95%CI 4.9-12.4), specific communication regarding pain (OR 2.3, 95%CI 1.3-4.1) and the administration of oral opioids (OR 2.0, 95%CI 1.1-3.4). Notably, the provision of nurse-initiated analgesia to 211 (44.3% ) patients and the short time to analgesia (median 11.5 min) were non-significant variables.

Conclusions: The ‘adequate analgesia’ target provides a highly valuable, clinically relevant and achievable endpoint for ED staff in the pursuit of best-practice pain management.
OBESITY HAS FEW ADVERSE EFFECTS ON THE PATIENTS' EXPERIENCE IN THE EMERGENCY DEPARTMENT

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²Medicine, University of Melbourne, Parkville, VIC, Australia

Objective: To determine if obesity (BMI >30.0kg/m²) adversely affects the patients' ED experience in terms of flow variables and rates of assistance, investigation and procedure.

Methods: This was a prospective, analytical, observational study in a large tertiary referral ED. Consecutive patients, presenting during data collection periods, were enrolled after they had received ≥3 hours of care. Height and weight data were collected from the patient; demographics, presenting complaint, triage category, time to be seen, and modes of arrival and disposition from the EDIS system; and investigations from the electronic pathology and radiology records. Data on a wide range of procedures and management variables were collected directly from the ED staff using a specifically-designed survey instrument.

Results: 711 patients were enrolled (mean age 64.3±18.6 years, 375 [52.7%] male). 191 (26.9%, 95%CI 23.7-30.3) patients were obese. Obese patients were significantly younger than non-obese patients (median 63 vs 70 years, p<0.001). They had significantly more IV cannulation attempts, liver function tests (69.1% vs 60.2%), cardiac enzyme tests (40.8% vs 30.0%) and abdominal X-rays (17.8% vs 8.7%), (p<0.05). There were no differences between the groups in time to be seen, monitoring, other procedures, assistance required, place of disposition, or ED length of stay (p>0.05). Interestingly, obese patients had a lower death rate during the study period (1.6% vs 7.5%, p<0.01).

Conclusions: Overall, obesity does not adversely affect the patients' ED experience. The observed differences in some investigation rates may relate to suspected morbidities and difficulties in physical examination.

PUBLIC HEALTH SCREENING IN THE EMERGENCY DEPARTMENT: AN EXTRA DIMENSION

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¹Emergency, Austin Health, Heidelberg, VIC, Australia
²Medicine, University of Melbourne, Parkville, VIC, Australia

Objective: To determine the prevalence of undiagnosed and undertreated hypercholesterolaemia and hypertension among ED patients and to evaluate the effects of a formal referral back to the GP for further management.

Methods: This was a prospective, cross-sectional study of ED patients with follow up, if indicated. Patients aged ≥35 years, without substantial illness or communication difficulties, were enrolled. Data were collected using a researcher-administered questionnaire, a point-of-care Accutrend® Plus machine and digital sphygmomanometer. Patients with total cholesterol (TC) ≥6.0 mmol/L and/or blood pressure ≥140/90 were given a referral letter and advised to see their GP. Follow-up telephone calls were made 5 weeks later.

Results: Of 827 presentations, 534 patients were enrolled (mean age 56.7±13.3 years, 300 [56.2%] male). 111 (20.7%, 95%CI 17.5-24.5 ) patients had TC ≥6.0 mmol/L; seven had immeasurably high levels. Patients with/without elevated TC differed significantly (p<0.05) in regard to age, gender, GP ownership and attendance, and previous screening. 66 patients followed up with their GP. 30 had their TC levels re-tested, 18 received dietary/lifestyle advice, two were commenced on cholesterol-lowering medication and another two had their medication regimens revised. 96 (18.0%, 95%CI 14.9-21.6) patients had hypertension (highest reading 240/149). 53 followed up with their GP. Investigations were ordered for three, medication started for four and medications altered for three.

Conclusions: Substantial proportions of ED patients have undiagnosed and undertreated hypercholesterolaemia and hypertension. GP referral initiated intervention for many patients. The ED may have a role in public health screening although dedicated staff would be required.
ARterial oxygen tension and mortality in mechanically ventilated patients

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⁷NZ Medical Research Institute, Wellington, New Zealand

Early hyperoxia may be an independent risk factor for mortality in mechanically ventilated patients. We retrospectively assessed arterial blood gases (ABG) to determine the ‘worst’ PaO₂ (PaO₂ with the highest A-a gradient if FiO₂ ≥0.5 at any time, or lowest PaO₂ if FiO₂ <0.5) during the first 24 hours of ICU admission for all ventilated adult patients from 150 ICUs between 2000-2009. We used multivariate analysis in all patients and defined subgroups to determine the relationship between worst PaO₂ and mortality. We also studied the relationship between worst PaO₂ in the first 24 hours, admission PaO₂ and peak PaO₂ in a random cohort of 200 patients.

We studied 152,680 patients. Their mean worst PaO₂ was 152.4 mmHg (SD 109.7), mean FiO₂ was 62% (SD 26), and 49.8% (76,110) had hyperoxia (PaO₂ >120 mmHg). Overall, 19% of patients died in ICU and 26% in hospital. After adjusting for site, SAPS II, age, FiO₂, surgical type, GCS<15 and year of ICU admission, there was an association between progressively lower PaO₂ and increasing in-hospital mortality, but not with increasing levels of hyperoxia. Similar findings were observed with a sensitivity analysis of high FiO₂ (≥50%) vs. low FiO₂ (<50%), and in defined subgroups. Worst PaO₂ showed a strong correlation with admission PaO₂ (r=0.98) and peak PaO₂ within 24 hours of admission (r=0.86).

We found there was an association between hypoxia and increased in-hospital mortality, but not with hyperoxia. Our findings differ from previous studies and suggest that the impact of early hyperoxia on mortality remains uncertain.

Haemodynamic impact of a slower pump speed at start of CRRT

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²ANZIC RC, Monash University, Melbourne, VIC, Australia

Critically ill adult patients with acute kidney injury (AKI) are at risk of haemodynamic instability when starting continuous renal replacement therapy (CRRT). We describe the haemodynamic impact of our “routine protocol” versus “slower” CRRT pump speed starts in such patients.

Using a prospective before and after design we compared data for “routine protocol” pump speed increases of 50 ml/min over 1 to 4 minutes with “slower” increases of 20-50 ml/min over 3 to 10 minutes to achieve an operating blood flow of 200 ml/min. We obtained patient demographic, haemodynamic, and vasopressor requirement data during the first 30 minutes of CRRT.

We studied 21 routine and 20 slower CRRT starts. ‘Routine protocol’ starts reached the target pump speed quicker than slower CRRT start (p <0.05). Heart rate was higher in the routine group compared to the slower group at baseline (p<0.01) and remained so throughout. There were no significant changes in CVP or MAP, and no episodes of hypotension or hypertension, in either group. In the subset of 17 (41%) CRRT starts in vasopressor dependent patients, no episodes of hypotension or hypertension were observed and heart rates remained within ±5% of the rate at the time of CRRT commencement.

A slower pump speed at the start of CRRT did not result in haemodynamic instability compared to our routine protocol start. Our findings differ from previous studies but may reflect our cautious pump speed approach in both groups. We recommend caution at the start of CRRT and advocate for close haemodynamic monitoring.
RENAL BIOMARKERS MAY BE OF LIMITED UTILITY IN THE GENERAL INTENSIVE CARE POPULATION.

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Multiple biomarkers have been proposed for identifying patients at risk of developing AKI. These biomarkers include urine and serum NGAL, and urinary hepcidin.

We sought to determine which biomarker was the most accurate in predicting AKI.

We measured serum and urinary NGAL and urinary hepcidin in patients admitted to ICU with SIRS and either oliguria or a 25 µmol/l serum creatinine increase within 48 hours of admission. We used point-of-care creatinine measurements to identify the maximum RIFLE category of AKI within the first five days of enrolment. We corrected both urinary biomarkers for urinary creatinine. We calculated the reciprocal of hepcidin measurement and noted if serum NGAL was greater than the upper limit of normal (149ng/ml). We derived the area under the curve (AUC) for the receiver operating characteristic curve (ROC) for all biomarkers.

Between 31/08/10 and 17/11/10, we enrolled 92 patients. The best predictors of any degree of AKI were urinary hepcidin (AUC=0.607) and serum NGAL positivity (AUC=0.589) (Table 1). The best predictors of RIFLE category I or F, were urinary NGAL (AUC=0.636), urinary NGAL corrected for urinary creatinine (AUC=0.654) and serum NGAL positivity (AUC=0.632) (Table 1).

TABLE 1: AUC ROC for the prediction of AKI

<table>
<thead>
<tr>
<th>Test Result Variable</th>
<th>ROC AUC</th>
<th>RIFLE R, I or F</th>
<th>RIFLE I or F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Area</td>
<td>Std. Error</td>
</tr>
<tr>
<td>Urinary NGAL</td>
<td>0.544</td>
<td>0.636</td>
<td>0.070</td>
</tr>
<tr>
<td>Urinary NGAL corrected for urinary creatinine</td>
<td>0.560</td>
<td>0.654</td>
<td>0.065</td>
</tr>
<tr>
<td>Serum NGAL</td>
<td>0.584</td>
<td>0.610</td>
<td>0.082</td>
</tr>
<tr>
<td>Serum NGAL positivity</td>
<td>0.589</td>
<td>0.632</td>
<td>0.073</td>
</tr>
<tr>
<td>Urine:Serum NGAL ratio</td>
<td>0.494</td>
<td>0.570</td>
<td>0.068</td>
</tr>
<tr>
<td>Urinary Hepcidin</td>
<td>0.393</td>
<td>0.419</td>
<td>0.069</td>
</tr>
<tr>
<td>1/Urinary Hepcidin</td>
<td>0.607</td>
<td>0.581</td>
<td>0.069</td>
</tr>
<tr>
<td>Urinary Hepcidin corrected for urinary creatinine</td>
<td>0.414</td>
<td>0.449</td>
<td>0.073</td>
</tr>
<tr>
<td>1/Urinary Hepcidin corrected for urinary creatinine</td>
<td>0.586</td>
<td>0.551</td>
<td>0.073</td>
</tr>
</tbody>
</table>

In this cohort of ICU patients the ability of NGAL and hepcidin to predict AKI is limited. Further investigation is needed on whether the combination of specific biomarker patterns and clinical features can better identify patients at risk.
NGAL as a marker of tubular damage appears to be unrelated to FENA as a marker of tubular function in patients with AKI.

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NGAL (neutrophil gelatinase-associated lipocalin) is a marker of renal tubular damage. FENA (fractional excretion of sodium) is a marker of renal tubular function. Insults damaging the tubules and resulting in AKI should both stimulate NGAL production and prevent resorption of sodium.

To test this hypothesis, we studied ICU patients developing SIRS and oliguria or a 25 µmol/l increase in serum creatinine within 48 hours of ICU admission. We sought to determine if a relationship existed between FENA and NGAL in patients developing AKI.

We measured the serum and urinary NGAL, creatinine and sodium of ICU patients with SIRS and either oliguria or an increase in creatinine within 48 hours of admission. Point-of-care creatinine measurements were used to identify the maximum RIFLE category of AKI developed within the first five days of admission. The strength of the relationship between variables was determined using Spearman's rank correlation co-efficient.

We enrolled 93 patients between 31/08/10 and 17/11/10. Serum NGAL and urinary NGAL when corrected for urinary creatinine were found to correlate moderately well with FENA in patients who did not develop AKI. A stronger correlation exists between corrected urinary NGAL and FENA among patients with RIFLE R AKI. No other correlation showed a significant relationship (Table 1).

TABLE 1: Relationships between NGAL, FENA and AKI

<table>
<thead>
<tr>
<th>FENA</th>
<th>N</th>
<th>Urinary NGAL</th>
<th>Urinary corrected for urinary Creatinine</th>
<th>Serum NGAL</th>
<th>Urine:Serum NGAL ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spearman's p</td>
<td>Spearman's p</td>
<td>Spearman's p</td>
<td>Spearman's p</td>
</tr>
<tr>
<td>No AKI</td>
<td>55</td>
<td>0.1324</td>
<td>0.3354</td>
<td>0.4810</td>
<td>0.0002</td>
</tr>
<tr>
<td>RIFLE R-F</td>
<td>38</td>
<td>-0.0096</td>
<td>0.9542</td>
<td>0.4170</td>
<td>0.0091</td>
</tr>
<tr>
<td>RIFLE R</td>
<td>19</td>
<td>-0.1887</td>
<td>0.4392</td>
<td>0.5170</td>
<td>0.0234</td>
</tr>
<tr>
<td>RIFLE I</td>
<td>13</td>
<td>-0.2637</td>
<td>0.3839</td>
<td>0.0549</td>
<td>0.8585</td>
</tr>
<tr>
<td>RIFLE F</td>
<td>6</td>
<td>0.1429</td>
<td>0.7872</td>
<td>0.3143</td>
<td>0.5441</td>
</tr>
</tbody>
</table>

The lack of a strong correlation FENA and NGAL in patients developing RIFLE I and F AKI suggests that changes in NGAL and changes in sodium resorption occur as a consequence of different stimuli in the pathogenesis of the syndrome.
URINARY HEPcidin is a marker of systemic inflammation in the setting of preserved kidney function.

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Hepcidin is released in response to situations which predispose to AKI and greater concentration in the urine has been associated with decreased risk of AKI. The relationship between serum creatinine, urinary hepcidin and CRP may help define whether urinary hepcidin is more likely to reflect systemic inflammation or renal events.

Patients with SIRS, oliguria and a 25 µmol/l increase from baseline creatinine are known to be at an increased risk of AKI. We sought to determine if hepcidin correlated more strongly with CRP or creatinine.

Patients meeting the inclusion criteria within 48 hours of admission had their CRP, urinary hepcidin, and serum and urinary creatinine measured. The strength of the relationship between serum creatinine or CRP and urinary hepcidin corrected for urinary creatinine was determined using Spearman's rank correlation co-efficient.

We enrolled 103 patients between 31/08/10 and 17/11/10. Serum creatinine only correlated weakly with direct and inverse urinary hepcidin measurements (Table 1). There was a modest correlation between CRP and urinary hepcidin measurements creatinine (Table 1).

TABLE 2: Relationships between hepcidin, creatinine and CRP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum Creatinine</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Hepcidin</td>
<td>-0.26 (p=0.007)</td>
<td>0.31 (p=0.001)</td>
</tr>
<tr>
<td>1/ Urinary Hepcidin</td>
<td>0.27 (p=0.005)</td>
<td>-0.30 (p=0.002)</td>
</tr>
<tr>
<td>Urinary Hepcidin corrected for urinary creatinine</td>
<td>-0.18 (p=0.06)</td>
<td>0.35 (p=0.0003)</td>
</tr>
<tr>
<td>1/Urinary Hepcidin corrected for urinary creatinine</td>
<td>0.19 (p=0.05)</td>
<td>-0.34 (p=0.0004)</td>
</tr>
</tbody>
</table>

Hepcidin is only weakly inversely correlated with serum creatinine. A stronger relationship exists between hepcidin and CRP, suggesting that hepcidin may primarily be a marker of inflammation which is filtered in the urine when glomerular filtration rate (GFR) is preserved and filtered in lower amounts when GFR is lost.
FENA IS NOT A USEFUL RENAL BIOMARKER IN THE CRITICALLY ILL.

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Fractional excretion of sodium (FENa) is thought to be a marker of renal tubular function. There have been no pragmatic assessments of its accuracy in predicting AKI as a renal biomarker.

To test this hypothesis, we studied ICU patients developing SIRS and oliguria or a 25 µmol/l increase in serum creatinine within 48 hours of ICU admission. We sought to determine if FENa was a useful biomarker for the development of AKI in a pragmatic study uncontrolled for the confounding variables experienced as part of routine ICU practice.

We measured urine and serum sodium and creatinine in patients meeting the inclusion criteria. We identified the maximum RIFLE category of AKI within the first five days of admission measure for each patient using point-of-care creatinine measurements. We derived the area under the curve (AUC) for the receiver operating characteristic curve (ROC) for FENa and FENa > 2%, indicating high urinary sodium excretion.

We enrolled 92 patients between 31/08/10 and 17/11/10. For FENa, the AUC = 0.589 for predicting RIFLE R to F, and AUC = 0.614 for RIFLE I or F. Predictive value was worse when only FENa > 2% were included (Table 1.).

<table>
<thead>
<tr>
<th>Variable</th>
<th>ROC AUC</th>
<th>RIFLE R, I or F</th>
<th>RIFLE I or F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Result</td>
<td>Area</td>
<td>Std. Error</td>
<td>Area</td>
</tr>
<tr>
<td>FENa</td>
<td>0.589</td>
<td>0.061</td>
<td>0.614</td>
</tr>
<tr>
<td>FENa &gt; 2%</td>
<td>0.552</td>
<td>0.062</td>
<td>0.522</td>
</tr>
</tbody>
</table>

In this cohort of ICU patients FENa is a poor biomarker of subsequent AKI. In the context of routine ICU practice, FENa is unlikely to be independently useful as a predictor of AKI.

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) HAS A STRONGER CORRELATION WITH SERUM CREATININE THAN C-REACTIVE PROTEIN.

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NGAL predicts the development of AKI amongst critically ill patients. It is unclear, however, whether this predictive relationship is due to the fact that NGAL is produced by neutrophils and is, therefore, a biomarker of inflammation or whether NGAL in blood and/or urine mostly reflects tubular release.

To test this hypothesis, we studied ICU patients with SIRS and oliguria or a 25 µmol/l increase in serum creatinine. We sought to determine whether blood and urine NGAL correlated more closely with CRP or creatinine at the time of enrolment.

The strength of the relationship between serum creatinine or CRP and urine, serum and urine:serum NGAL was determined using Spearman's rank correlation co-efficient.

We recruited 105 patients between 31/08/10 and 17/11/10. NGAL in blood or urine correlated only weakly with CRP. In contrast, the correlation between serum and/or urine NGAL and serum creatinine was stronger, and statistically significant.

TABLE 1: Relationships between NGAL, creatinine and CRP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum Creatinine</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary NGAL</td>
<td>0.39 (p&lt;0.0001)</td>
<td>0.24 (p=0.016)</td>
</tr>
<tr>
<td>Urinary NGAL corrected for urinary creatinine</td>
<td>0.55 (p&lt;0.0001)</td>
<td>0.09 (p=0.37)</td>
</tr>
<tr>
<td>Serum NGAL</td>
<td>0.46 (p&lt;0.0001)</td>
<td>0.22 (p=0.027)</td>
</tr>
</tbody>
</table>

NGAL is only weakly correlated with CRP. A stronger relationship exists between NGAL and serum creatinine. This suggests that, NGAL is more likely a biomarker of tubular injury or stress than systemic inflammation.
RENAL PERFUSION EVALUATION BY CONTRAST ULTRASOUND AFTER CARDIAC SURGERY, A PILOT STUDY

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²Radiology department, Austin Health, Heidelberg, VIC, Australia

Background: Acute kidney injury (AKI) is a frequent and severe complication of cardiac surgery but its pathophysiology is, to date, poorly understood. We performed a pilot study to evaluate changes in renal blood flow (RBF) in patients deemed at risk for acute renal injury using contrast ultrasound (CEUS). The aim of the study was to establish the feasibility and safety of CEUS in the peri-operative period.

Methods: We recruited five patients deemed at risk of AKI and scheduled for elective cardiac surgery. CEUS with destruction-replenishment sequences was performed before and at six and 24 hours after the surgery. At each study time, 6 sequences were obtained. These sequences, recorded in DICOM format, were then analyzed using Sonotumor™, a dedicated software, by two senior radiologists blinded to the sequence.

Results: All examinations were well tolerated and no issues were raised regarding the feasibility of the CEUS in post-operative patients. We found very good agreement in between the two radiologists (r=0.92 p<0.001). The perfusion indices are presented in the Figure 1.

Conclusions: CEUS is feasible and well tolerated in the critically including just after cardiac surgery. Data analysis has good inter-observer agreement. Further data is required to draw conclusions regarding changes in RBF after cardiac surgery.

SEVERE ACUTE KIDNEY INJURY NOT TREATED WITH RENAL REPLACEMENT THERAPY: CHARACTERISTICS AND OUTCOME

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²Intensive Care Unit, Jikei University School of Medicine, Tokyo, Japan

Introduction: Only a proportion of critically ill patients with severe (RIFLE class-F) AKI appear to receive renal replacement therapy (RRT).

Objectives: To study the epidemiology of patients with severe (RIFLE-F) AKI who did not receive RRT.

Methods: We identified all consecutive patients admitted to our institution that developed RIFLE-F AKI by creatinine criteria over a three-year period and did not receive RRT and compared their characteristics and outcomes with those of RIFLE-F RRT-treated patients.

Results: Within the study period, 20126 patients were admitted in our institution for more than 24 hours including 2949 in the intensive care unit (ICU). Among them, 195 developed RIFLE-F AKI: 90 received RRT (RRT-patients) and 105 did not (no-RRT-patients). Compared with RRT-patients, no-RRT patients were similar in terms of age, gender and ward of origin but had a shorter median ICU stay (2.7 vs. 7.9 days; p=0.001), required less mechanical ventilation (56.2% vs. 70%; p<0.05), and had a lower mean APACHE III score (82.7 vs. 86.7, p<0.05). The two main reasons these patients did not receive RRT were limitations of medical therapy (LOMT) in 41(39%) cases and expected renal recovery in 59 (56.2%). Mortality in no-RRT patients was 58.1% compared with 55.5% in the RRT group (p=NS). After exclusion of LOMT patients, however, overall mortality was lower in the no-RRT group (30.5% vs. 55%; p<0.001).

Conclusions: After exclusion of LOMT patients, more than a third of critically ill patients with severe (RIFLE-F) AKI did not receive RRT. A third of these patients died in hospital.
COMPARISON BETWEEN FLUID BALANCE AND CHANGES IN BODY WEIGHT IN THE CRITICALLY ILL PATIENT
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Background: Fluid status evaluation is important in critical illness. It is usually assessed by physical examination and the calculation of a fluid balance obtained by subtracting the volume of fluids excreted to that of fluids administered. Measuring patients' body weights, though considered the gold standard, has been extremely cumbersome. Recently, hospital beds with the ability to weigh patients directly have become available. We sought to compare results obtained by these two methods in “real life” critically ill patients.

Methods: Between November 2010 and May 2011, all patients admitted in our intensive care unit for more than two consecutive days and nursed on a Hill-Rom Total Care® bed were weighed daily at 2400 hrs. Fluids charting was done with an electronic spreadsheet with 2400 hrs calculation (SLIC software V?). Differences in weights and fluid balance between two consecutive days were compared using correlation analyses and Bland-Altman plot. Corrections for unmeasured fluids losses were performed using a pre-determined formula based on peak temperature and intubation status.

Results: We obtained complete data in 160/504 admissions exceeding 2 days (153 patients) resulting in 435 data points. The difference in weights and the result of the fluid balance were only weakly correlated (r=0.37, p<0.001, Fig.1) even after correction for insensible fluid losses (r=0.36, p<0.001). The Bland-Altman plot (Fig.2) revealed proportional error but no systematic bias.

Conclusions: The low correlation between change in weight and change in fluid balance suggest that both these tools of fluid status monitoring have limited accuracy. They must be interpreted with caution.

AN AUDIT OF ANALGESIA PRACTICES FOR FRACTURED NECK OF FEMUR PATIENTS IN THE AUSTIN HEALTH EMERGENCY DEPARTMENT
M. Ward, D. Yeoh
Emergency, Austin Health, VIC, Australia

Aim:
To ensure patients who present to The Austin Emergency Department with fractured neck of femur (# NOF) receive optimal pain management as per best practice guidelines.

Methods: Retrospective chart review of all admissions with # NOF over 4 months (from 1/12/2010 to 8/05/2011) specifically looking at analgesia practice. Data collected will be compared to previous audit results and to best practice guidelines which state that all # NOF patients should receive a nerve block (Macintyre et al 2010)

Results: There were 101 # NOF patients identified, with 97 having records available for audit.

- The median waiting time was 31min and median LOS in the ED was 6.9h
- 52% of patients had a nerve block with median time from triage 2h (36% and 2hr 30 min in 2010, nil pain blocks administered in 2007 audit)
- 69% of patients were given parenteral morphine with median time from triage 47min (63% and 1hr 30min in 2010)

Conclusions: These most recent results indicate significant improvement from 2007 with the use of nerve blocks rising from 0% in 2007 to 36% in 2010 and 52% in the current audit. Analgesia for # NOF patients continues to improve with 80% of patients receiving a nerve block or peripheral morphine and having a median final pain score of 1/10.

DEVELOPMENT OF A WEB BASED PORTAL FOR RECORDING AND REVIEWING POSTGRADUATE NURSING EXPERIENCE IN ICU.
I. C. Baldwin, N. G. Fealy, P. M. Carty, M. Farrell
ICU, Austin Health, Heidelberg, VIC, Australia

Recording clinical experience for each nursing shift in ICU has the potential to improve post graduate training. Review of data collected can direct learning opportunities to meet minimum skill sets and ensure equity. There is no published data describing clinical experiences completed during post graduate programs. We designed and implemented a web based portal enabling nurses in post graduate training to record every shift experience. With ethics approval we reviewed data from this activity after 2 cohorts; 2009 and 2010 intakes.

Microsoft Sharepoint software was used to create a web based clinical experience portal (CEP) accessible via wireless hand held or bedside computers. Each shift, nurses used a unique log-in to record their shift experience into a prepared tick box data base. Patient category, shift (D/E/N) and procedures done were key data entries completed.

1319 shift entries were made over 2 years by 2 groups of students (n=26). 578 day, 612 evening and 129 night shifts. Surgical 700 and medical 559. Key data from the database was; cardiac surgical acute post op; 302 cases, respiratory failure 192, neuro surg 159, liver fail/transplant 149. Procedures; extubations 132, intubations 19, pulmonary artery catheter removal 42, CRRT priming 96 and ‘family meeting’ 44.

Recording every shift experience in post graduate nursing training provides useful information to better standardize experience across groups and establish minimal skill sets necessary for ensuring competency in future programs.

AN AUDIT OF WRIST FRACTURE MANAGEMENT IN THE AUSTIN HEALTH EMERGENCY DEPARTMENT
M. Ward, M. Yeoh
Emergency, Austin Health, VIC, Australia

Aim/Rationale: To review the management of patients diagnosed with fractured wrists within Austin Health ED.

Methods: Retrospective chart review for all patients with ED discharge diagnosis of “fractured wrist” for period 1/6/2010 to 31/05/2011. Data to be compared to previous audit results and externally published data.

Results: - 632 patients were discharged from ED with a diagnosis of fractured wrist (previous audit 525);
- 5.2% of patients that were discharged home post treatment in ED required admission for unplanned reduction (ORIF/GAMP) (3.8% previously);
- 1.1% of wrist fractures were treated post prior discharge without intervention (previously 0.6%)
- 179 closed reductions in ED
  o Those aged 65 and over were more likely to receive a LAMP in ED (40% compared to 25% in other age groups)
  o 10.6% of fractures post closed reduction required unplanned ORIF/GAMP (previously 8.1%).
- 294 POPs/backslabs without manipulation
  o 8 (2.1%) were d/c with POP without ORTH advice and subsequently required ORIF/GAMP post OP review (previously 5, 1.8%)
- 109 pts had ORIF/GAMP
  o Adults aged 18-65 were more likely to have a planned ORIF/GAMP (17% compared to 9 and 11% in paediatric and 65 + groups respectively)
  o 77 were planned ORIF/GAMP
  o 27% (n=29) were unplanned either post LAMP or backslab (previously 22% n= 20)

Conclusions: Although the percentage of patients who had a fracture missed or who required unplanned intervention post reduction of a fractured wrist has risen marginally since last review, the fraction remains clinically acceptable in relation to available evidence (Rhemrev et al 2009, Wei et al 2005, Pallai et al, 2005).

AN AUDIT OF APPENDICITIS MANAGEMENT IN THE AUSTIN HEALTH EMERGENCY DEPARTMENT

M. Ward, M. Yeoh

Emergency department, Austin Health, Heidelberg, Australia

Aim: To review the management of patients with suspected appendicitis at Austin ED

Methods: Retrospective chart review was conducted for period 1/05/2010 to 30/04/2011 for all patients with discharge diagnosis of “acute appendicitis”. Results were compared to a previous 2007/2008 audit and externally published data.

Results: 337 patients had a discharge diagnosis of “Appendicitis” (previous audit; 339)

- 7 were representations (previously 13 representations)
- A total of 280 (previously 252) patients went to theatre, with 74% having acute appendicitis
- 226 (67%) of those who went to theatre had confirmed Appendicitis on histology (previously 60%)
- Of the 54 paediatric patients nil were transferred out to other hospitals (previously 25%).
- 29 (54%) of the paediatric patients who went to theatre at Austin and had the diagnosis confirmed (55% previously)

Conclusions: Of 4139 patients with abdominal complaints discharged from the ED just 7 (0.17%) returned and were admitted with acute appendicitis. This is an improvement on previous audit results of 13 in 3350 (0.4%) – this ratio reflects an acceptable balance of returns versus unnecessary admissions. Of those who went to surgery 30 (11%) were not diagnosed with acute appendicitis and could be categorised as negative exploration. This is comparative to other published data which reports a negative exploration rate of around 15-22% (Myers et al 2009, Hlibczuk et al 2010). The transfer rate for paediatrics which was previously high has now resolved to zero.

SARCOPENIA AND VITAMIN D DEFICIENCY ARE RISK FACTORS FOR FALLS BUT REMAIN UNDETECTED IN AGED CARE RESIDENTS

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Institutionalised elderly, in whom sarcopenia and vitamin D deficiency are common, are at high risk for falls. We aimed to determine the contribution of sarcopenia and vitamin D deficiency to falls risk and to identify ways of assessing the risk of falling in elderly aged-care residents. 80 ambulatory female residents age 86 years (range 67-99 years) from 18 low-level aged care facilities participated. Body composition was determined using DXA, ankle, knee and hip strength measured using the Nicholas manual muscle tester, balance assessed using the Lord's Balance test, and physical function reported using TUG and walking speed over 6 metres. Serum 25(OH)D was measured from morning blood samples. Basic anthropometry was performed. Falls were recorded prospectively during 12-months. Medical records were reviewed for medical conditions and medication use. Relative sarcopenia was determined using the Janssen method. Chi square distributions and logistic regression analysis were performed. Sarcopenia was associated with an increased risk for falls (OR 10.7; 95% CI 1.1–99.9, p<0.05). Higher serum 25(OH)D levels had a small but protective effect against risk for falls (OR 0.97; 95%CI 0.94–0.99, p<0.05). Age, strength, function, balance, and number of medications or medical conditions were not predictors for falls. Sarcopenic women were heavier (but not taller), had higher BMI (27.8 ± 4.3 v 22.1 ± 2.4, p=0.001) and had greater % body fat (40.8 ± 5.4 v 26.2 ± 5.1, p<0.001) than non-sarcopenic women, but groups did not differ in lean mass. Sarcopenic women were not distinguishable using limb circumferences or functional measures, and despite being sarcopenic most were in the overweight to obese weight range. Sarcopenia is a risk factor for falls but is not readily identified from basic anthropometry therefore goes undetected. Routine screening of serum 25(OH)D levels and correction of deficiencies may also contribute to falls risk reduction in elderly aged care residents.
SAFE, EFFECTIVE USE OF A VERY LOW ENERGY DIET IN AN OBESE ELDERLY INPATIENT.

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Mr. RL, aged 68, presented to hospital with infected venous ulcers on both legs. He had a Body Mass Index (BMI) of 43.4kg/m² and multiple obesity related comorbidities including type 2 diabetes and osteoarthritis. He required the assistance of 3 people for mobility and personal hygiene. In hospital, he refused physiotherapy and ate large quantities of junk food. After 3 weeks with no functional gains, he was informed that a nursing home would be the likely discharge destination. Subsequently, his motivation improved and he was offered rehabilitation.

On transfer, the patient was commenced on a Very Low Energy Diet (VLED – Optifast®). This included a sachet of Optifast® for breakfast and lunch, and lean protein with leafy vegetables for dinner, with 9g/day L-arginine and 500mg Vitamin C supplements. Over 10 weeks, his weight decreased to 97kg (BMI 33.6kg/m²). On discharge home, he was able to independently toilet, shower and walk 40 metres with a frame. His leg ulcers improved, and his serum nutritional parameters remained unchanged.

Obesity in older inpatients with wounds presents a management challenge. Obesity is associated with increased rates of functional decline and frailty, and intentional weight loss may reverse these. In the morbidly obese, wounds can be more severe and there may be micronutrient deficiencies. Recommendations to increase overall caloric intake may not be appropriate; instead, it may be appropriate to focus on nutrients important for wound healing. VLEDs are formulated, nutritionally complete dietary regimens containing less than 800kCal/day. There is extensive evidence for their use in younger adults, but are relatively contraindicated in those over 65. There is evidence for the use of arginine supplementation in wound care.

This case illustrates that closely supervised weight loss achieved with the aid of a VLED and supplements is compatible with wound improvement, and may help improve physical function.

THE IMMUNOPROTEASOME IS EXPRESSED BY LYMPHOCYTES AND PLAYS CRITICAL ROLES IN LYMPHOCYTE DEVELOPMENT

D. J. Zanker, K. C. Pang, W. Chen

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The immunoproteasome differs from the housekeeping proteasome through the substitution of the catalytically active β1, β2 and β5 subunits for LMP2, Mecl-1 and LMP7, respectively. As LMP2 and LMP7 are encoded by genes localised in the class-II region, the major function of the immunoproteasome is proposed to enhance MHC class-I-restricted antigen processing and presentation by providing peptides that are tailor-made for binding to class-I. Interestingly, LMP2-/- mice not only have an altered T cell repertoire, but also have significantly reduced thymocytes and peripheral lymphocytes, which is not easily explained according to its proposed role.

To explore the underlying mechanisms, we compared thymocytes and splenocytes from wild-type C57B/L6 and LMP2-/- mice. In the periphery, LMP2-/- mice have decreased lymphocytes but normal numbers for other bone marrow derived cell types, such as DCs and macrophages. In the thymus, staging analysis indicated a developmental halt, accompanied with increased apoptosis, at the CD4CD8- (DN) stage at the transition from DN3 to DN4. Similarly, a developmental halt was found in the B cell lineage at the immature to T1 B cell transition. We confirmed by Western Blot that both developing wild-type T and B cells express immunoproteasome subunits. The NFκB pathway is known to play an important role in lymphocyte survival at these developmental stages. The abundance of various NFκB proteins was investigated by Western blot and confocal microscopy in the presence or absence of pathway activation using TNFα.

Subsequently, we detected decreased degradation of IkBα and precursor proteins p105 and p100 in developing lymphocytes from LMP2-/- mice, which together would result in decreased survival. Together, these results provide a link between the immunoproteasome and the NFκB pathway at crucial lymphocyte developmental stages. We have therefore demonstrated the immunoproteasome also plays important biological, housekeeping roles other than simply enhancing antigen processing.
SYSYSTEMATICALLY EXPLORING THE CONTRIBUTION OF INDIVIDUAL IMMUNOPROTEASOME SUBUNITS TO INFLUENZA CD8⁺ T CELL REPERTOIRE AND EPITOPE ABUNDANCE

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The immunoproteasome is a specialised piece of protein degradation machinery that is reported to enhance MHC Class I-restricted antigen processing and presentation. The immunoproteasome differs from the housekeeping proteasome through the substitution of the catalytically active β1, β2 and β5 subunits for LMP2, Mecl-1 and LMP7 respectively, which alters the cleavage specificity.

To explore the contribution of each individual immunoproteasome subunit during an Influenza A virus (IAV) CD8⁺ T cell response, we used biochemical and functional assays to assess the impact of loss of 1 or 2 subunits on T cell repertoire, epitope abundance and epitope presentation. Polyclonal PR8-specific CD8⁺ T cell lines were generated from either wild-type, LMP2⁻/⁻, LMP7/Mecl-1⁻/⁻ or Mecl-1⁻/⁻ mouse strains, and T cell repertoire was assessed with 41 previously identified epitopes. Immunoproteasome deficient lines were observed to have a distinctly altered T cell repertoire, with various immunodominant and sub-dominant responses enhanced, decreased or absent.

Epitope generation and abundance was explored using naturally processed peptides derived from immunoproteasome subunit deficient bone-marrow derived dendritic cells, which were separated via HPLC. Distinct differences in specific-peptide abundance were observed for a variety of epitopes, including a dependence on individual immunoproteasome subunits for certain epitopes. Single specificity T cell lines were also used to ascertain the peptide quantity and kinetics of presentation of specific epitopes. Our results showed that individual immunoproteasome subunits greatly influenced the antigen processing and presentation of various peptides leading to different thymic selection of T cell repertoire as well as dramatically skewed CD8⁺ T cell responses.

Our study is the first systematic in vivo and biochemical characterisation of the contribution of individual immunoproteasome subunits to CD8⁺ T cell repertoire and peptide generation in an IAV model. The knowledge may help us to induce desired immune responses through manipulating the expression of various immunoproteasome subunits in future vaccines.

AN OPTIMISED CULTURE METHOD FOR ESTABLISHING MURINE CD8⁺ T CELL LINES

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CD8⁺ T lymphocytes, otherwise known as cytotoxic ‘killer’ T cells, are highly specific effector cells which can target and kill virally-infected or cancerous cells. These cells are able to identify extremely low amounts of foreign protein or tumour-derived protein fragments on target cells, which result in target-cell lysis. CD8⁺ T cells also play a key role in anti-tumor immunity, and because of this, are an integral part of immunotherapeutics into the cure of cancers. In vitro use of established, high purity T cell lines have proven to be an invaluable part of assessing CD8⁺ T cell repertoire, avidity and antigen processing and presentation.

Whilst routinely practiced for decades, in vitro T cell culture to date has largely been an impecrpal, individual laboratory-specific process. As a result of that, the outcome of such cultures has been inconsistent. Here, we outline a new method in which we have carefully optimized stimulating conditions, including antigen dose, IL-2 concentration, and depletion of unwanted B220⁺ cells of apoptotic phenotype. We show that high IL-2 concentration directly affects the purity and affinity of cultured T cells. Furthermore, high IL-2 concentration causes CD8⁺ T cells to express surface B220, undergo an apoptotic process and become less responsive to their cognate antigen. With optimized conditions, we are now able to reproducibly culture high affinity, high purity and single specificity CD8⁺ T cell lines specific to both immunodominant and subdominant T cell epitopes.
BROAD CROSS REACTIVITY OF CD8+ T CELLS OBSCURES EPITOPE IDENTIFICATION
D. J. Zanker, R. Lata, R. Murphy, W. Chen
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T cell repertoire is selected according to self peptides complexed to self MHC molecules in the thymus. Although most peripheral T cells recognize specific pathogen-derived antigenic peptides complexed to self-MHC exclusively, some have been reported to demonstrate cross-reactivity to either self or other peptides of foreign origin. It is also documented that T cells may cross-react to an entirely different MHC/peptide complex from the one it was intended to recognize. T cell cross-reactivity has been attributed to various autoimmune conditions and therefore it is vital to better understand such an interaction.

We show here that CD8+ T cells specific for a peptide derived from influenza A viral polymerase basic protein 2 (PB2), was able to react with multiple peptides of different length sharing a core sequence. As a result of such cross-reactivity and due to the minimum epitope containing a cysteine residue which is prone to post-translational modification, the characterization of the minimal epitope was not complete in the original publication. Our data emphasize the importance of detailed and quantitative assessments for such T cell specificity. Our data also highlights the importance of biochemical demonstration of the naturally presented minimal epitope.

Furthermore, we show that a previously described mimotope, a peptide that is only able to drive cross-reactive T cells without the capacity to stimulate a genuine response, was not only generated by cells that lack the immunoproteasome subunits LMP7 and Mecl-1, but also stimulated a subdominant T cell response in these mice. We therefore demonstrate mimotope—epitope switching due to the presence or absence of two individual immunoproteasome subunits.

POLYCLONAL T-CELL RECEPTORS RECOGNISE AN UNUSUALLY LONG TUMOUR ANTIGENIC PEPTIDE COMPLEXED TO HLA-B7
This abstract has not been included at the request of the author.

THE INITIATION OF THE CELLULAR IMMUNE RESPONSE TO CUTANEOUS MELANOMA
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The literature indicates T lymphocytes play a pivotal role in the control and clearance of melanoma. However, clinical trials have demonstrated that only 35% of melanoma patients treated with specific, tumour-reactive, tumour infiltrating T cells achieve either partial or complete tumour regression. This is due to the fact that malignant tumours evade recognition by the immune system and possess immunosuppressive factors preventing effective immune responses. This phenomenon is termed immune tolerance. Dendritic cells (DC) have been identified as key mediators in promoting effective immunity and enforcing immune tolerance. These cells acquire peripheral information and govern ensuing immunological responses. For example, DC have the capacity to educate T cells thereby instructing them to either remain silent (tolerance) or to fight unwanted malignancies (immunity). Thus, DC are a pivotal portal of communication in promoting effective T cell responses against cancerous cells. Currently, transplantable mouse melanoma models are widely used to examine the underlying mechanisms involved during tolerogenic processes in cancer. Furthermore, these models enable scientists to elucidate procedures with the potential to override this condition of tolerance leading to decreased tumour burden. However, a major caveat of these models is that routine experimental tumour inoculation occurs just below the skin (in the subcutaneous tissue). As melanoma is a topical skin (cutaneous) disease, we believe that cutaneous inoculation provides an improved model to investigate the pathology and the resulting immunological consequence. This is especially important in DC biology considering subtypes of these cells with specialised attributes reside in specific locales throughout an individual. We have established a novel small animal melanoma model that involves the transplantation of syngenic melanoma cells directly onto the skin. Using this model, we are investigating the ability of specific DC subsets to present melanoma-derived antigens to CD8+ T cells as well as evaluating the consequence of these interactions.
INCREASED MORTALITY IN PATIENTS WITH S. AUREUS BACTEREMIA ISOLATES WITH ELEVATED VANCOMYCIN MINIMUM INHIBITORY CONCENTRATION (MIC) PERSISTS AFTER ADJUSTMENT FOR COMORBIDITIES.

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Background: We recently reported that 30-day mortality in patients with S. aureus bacteremia (SAB) was correlated with elevated vancomycin (V) MIC even if their isolate was methicillin susceptible (MSSA) and they were treated with flucloxacillin (F). We investigated this surprising result by searching for hidden confounders in a subset of our original patients.

Methods: Additional clinical data were obtained from patients selected from a previously described Australasian cohort with SAB treated with V or F from January 2007 to November 2008.

Results: 418 patients were analysed (MRSA, 35%; hospital onset, 43%; 30d mortality, 18%; V treated, 45%). High V Etest MIC (> 1.5µg/mL) was present in 33% of all patient isolates and 25% of the MSSA subset treated with F. APACHE II and SAPS II scores were similar between low and high V MIC groups. Pitt bacteremia score was ≥ 4 in 21% and modified Charlson comorbidity index was ≥ 3 in 39%. When included in multivariate logistic regression, age, high V Etest MIC, Pitt bacteremia score and ICU admission were associated with increased mortality. The association between high V Etest MIC and mortality persisted in MSSA patients treated with F. Prior receipt of V was not associated with V MIC.

Conclusions: We have confirmed previous reports that V Etest MIC > 1.5µg/mL is associated with higher mortality in patients with SAB even after adjustment for potential confounders. As this risk persists regardless of which antibiotic is used we conclude that V Etest MIC > 1.5µg/mL marks but does not explain the increased mortality risk.
VANCOMYCIN PHARMACODYNAMICS IN STAPHYLOCOCCUS AUREUS BACTEREMIA (SAB).

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⁸Infectious Diseases, Royal Hobart Hospital, Hobart, TAS, Australia
⁹Microbiology, Auckland District Health Board, Auckland, New Zealand
¹⁰Medicine, University of Melbourne, Parkville, VIC, Australia
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Background: Vancomycin (V) minimum inhibitory concentration (MIC) may differ between testing method. V area under the curve (AUC)/MIC ≥ 400 using broth microdilution (BMD) has been associated with success in methicillin resistant S. aureus (MRSA) pneumonia and is recommended when treating serious S. aureus infection with V. We evaluated V AUC/MIC using BMD and Etest in patients with SAB.

Methods: Patients receiving V for SAB were selected from a previously described Australasian cohort. Creatinine clearance (CrCl) was calculated by Cockcroft-Gault (CG) equation and Modification of Diet in Renal Disease (MDRD) formula. AUC was calculated using V dose (mg per 24h)/[(CrClx0.79)+15.4]x0.06.

Results: 187 patients were treated with V for SAB were selected from a previously described Australasian cohort. Creatinine clearance (CrCl) was calculated by Cockcroft-Gault (CG) equation and Modification of Diet in Renal Disease (MDRD) formula. AUC was calculated using V dose (mg per 24h)/[(CrClx0.79)+15.4]x0.06.

Results: 187 patients were treated with V for SAB. Modal V MIC was BMD 1µg/mL or Etest 1.5µg/mL. CG or MDRD gave similar AUC results. V AUC/MIC was higher using BMD compared with Etest (Table 1). There was no difference in AUC/MIC between MSSA and MRSA. In patients including those with V Etest MIC >1.5µg/mL, and was not associated with lower 30-day mortality, reduced duration of bacteremia or risk of relapse.

Conclusions: · MIC method is important for V pharmacodynamics. As BMD is not routinely performed, AUC/MIC parameters may need revision for Etest.
· Achieving V AUC/MIC ≥ 400BMD was not associated with reduced mortality from SAB.

Differences in V AUC/MIC according to CrCl equation and MIC method

<table>
<thead>
<tr>
<th>MIC method</th>
<th>CrCl equation</th>
<th>V AUC/MIC, median</th>
<th>V AUC/MIC, IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>MDRD</td>
<td>433</td>
<td>308-650</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>427</td>
<td>292-655</td>
</tr>
<tr>
<td>Etest</td>
<td>MDRD</td>
<td>276</td>
<td>187-376</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>265</td>
<td>160-356</td>
</tr>
</tbody>
</table>

MARKED REDUCTIONS IN RATES OF VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE) COLONISATION & DISEASE ASSOCIATED WITH INTRODUCTION OF A ROUTINE HOSPITAL-WIDE BLEACH CLEANING PROGRAM

This abstract has not been published at the request of the author
VALIDATION OF NEW BINAXNOW STAPHYLOCOCCUS AUREUS AND PBP2A TESTS PERFORMED DIRECTLY FROM BLOOD CULTURES

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BACKGROUND: Rapid detection of both Methicillin-sensitive (SA) Staphylococcus aureus and Methicillin-Resistant (MRSA) bacteraemia significantly improves patient outcome. Two rapid tests SA and penicillin binding protein 2a (PBP2a) is now available. This study compared these tests with the routine in-house protocol of direct tube coagulase (DTC) and modified direct PBP2a test (PB) from blood cultures (BC).

METHOD: From October to December 2010, 85 BACTEC BC with GPC resembling staphylococci in the Gram stain were included. The first positive bottle for each patient was tested. DTC, BSA, BPBP and PB were done. There were 30 Staphylococcus aureus (STAU) and 7 were methicillin resistant (MRSA) and 55 Coagulase negative Staphylococci (CNS). Isolates were confirmed by routine testing.

S. aureus test (SAT): Briefly the BC was mixed with solution A, centrifuged, supernatant removed and washing repeated. Reagent B were added to the deposit and mixed, Reagent C was then mixed in. The sample was added to device with addition of fourth reagent. The result was read after 10 minutes.

PBP2a test (PB): briefly solution 1 was mixed with BC broth, centrifuged, supernatant removed and second reagent added, mixed and Reagent 3 added, mixed and centrifuged. Supernatant was added to the device and read at 10 minutes.

RESULTS: Twenty-two of 23 STAU and all seven MRSA were SAT positive. All CNS were SAT negative. Seven MRSA were BPBP positive and all SA negative. The sensitivity and specificity, Positive Predictive Value and Negative predictive Value of the SAT was 97%, 100%, 100% and 98% respectively and all 100% for BPBP test.

CONCLUSIONS: The SAT and BPBP are fast and reliable alternatives for direct detection from BC. It is useful for those laboratories without molecular facilities. The study should be expanded to include more patients particularly those with MRSA.
FOSFOMYCIN SUSCEPTIBILITY OF MULTI-RESISTANT BACTERIA BY ADS AND ETEST MIC

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BACKGROUND: Fosfomycin (FOS) has been used for treatment of uncomplicated urinary tract infections. There is renewed interest in FOS for treatment of multi-resistant infections. No susceptibility data is available in Australia. This study aimed to determine susceptibility in multi-resistant bacteria, and compare Etest (ET) with agar dilution (AD) methods for detection of resistance.

METHODS: There were 113 Gram positive cocci and 151 Gram negative bacilli. Included were Enterococci (EC); Staphylococcus aureus methicillin susceptible (ST) resistant (MR) and hetero vancomycin resistant (HV). Enterobacteria (EN) included producers of extended-beta-lactamases producers (ESBL) and plasmid-mediated AmpC (PAC); NF included Pseudomonas aeruginosa (PS) and Stenotrophomonas maltophilia (STM). RESULTS: GPC and GNB by AD and ET had 97% and 91%, 97% and 96% agreement respectively using CLSI and EU. Results are shown in the table below.

<table>
<thead>
<tr>
<th>Organism</th>
<th>AD</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLSI</td>
<td>EU</td>
</tr>
<tr>
<td>All GPC</td>
<td>113</td>
<td>11 (10)</td>
</tr>
<tr>
<td>EC</td>
<td>63</td>
<td>10 (16)</td>
</tr>
<tr>
<td>ST</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>MR</td>
<td>35</td>
<td>1 (3)</td>
</tr>
<tr>
<td>HV</td>
<td>17</td>
<td>1 (6)</td>
</tr>
<tr>
<td>All GNB</td>
<td>150</td>
<td>28 (19)</td>
</tr>
<tr>
<td>EN</td>
<td>79</td>
<td>6 (8)</td>
</tr>
<tr>
<td>ESBL</td>
<td>47</td>
<td>1 (2)</td>
</tr>
<tr>
<td>PAC</td>
<td>23</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ALL NF</td>
<td>73</td>
<td>20 (27)</td>
</tr>
<tr>
<td>PS</td>
<td>34</td>
<td>11 (32)</td>
</tr>
<tr>
<td>STM</td>
<td>25</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Etest is an alternative method. Resistance was very low except in PS and STM. Very low resistance, especially in multi-resistant ESBL, make FOS treatment of uncomplicated urinary tract infections, especially in outpatients, attractive.
IS DOXYCYCLINE EQUIVALENT TO MACROLIDES WHEN COMBINED WITH BETA-LACTAMS FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA?

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*Infectious Diseases, Austin Health, Heidelberg, VIC, Australia*

Background: Little data is available comparing the clinical efficacy of doxycycline vs. macrolides when combined with beta-lactams in empiric therapy of community-acquired pneumonia (CAP) as recommended in many international and Australian guidelines.

Methods: The Australian CAP Study (ACAPS) was a prospective, multicentre study of 885 episodes of CAP. Analysis of the recorded initial choice of antibiotic agents, in particular doxycycline or macrolide in combination therapy with a beta-lactam antibiotic and the relevant clinical outcomes of need for intensive respiratory and vasopressor support (IRVS), death, time to clinical stability and length of stay (LOS), was performed.

Results: Overall, patients treated with combination therapy containing doxycycline had a lower rate of IRVS ($p<0.001$), shorter time to clinical stability ($p=0.006$) and median LOS ($p<0.001$) compared to patients who received macrolide containing combinations. The two treatment groups were age matched and had no significant difference in clinical severity at presentation. A similar finding was noted in those with an atypical aetiology. In episodes due to known bacterial pathogens, there was no difference in outcomes.

Conclusions: Regardless of aetiology, the use of doxycycline in combination with beta-lactams for the treatment of CAP resulted in outcomes for time to clinical stability, LOS and, need for respiratory or vasopressor support that were at least as good as those in patients receiving macrolides. Doxycycline in combination with a beta-lactam is suitable as first line therapy for the empiric treatment of CAP.

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IMPROVING ORDERING OF C-REACTIVE PROTEIN (CRP) TESTING AT AUSTIN HEALTH – AN AUSTIN BY DESIGN PROJECT

P. G.P. Charles, L. Wright, C. O'Callaghan

*Infectious Diseases, General Medicine, or Strategy, Quality & Service Redesign, Austin Health, Heidelberg, VIC, Australia*

Improving ordering of C-reactive protein (CRP) testing at Austin Health – an Austin by Design project

Dr Patrick G.P. Charles, Lisa Wright, Chris O'Callaghan

1 Department of Infectious Diseases
2 Department of General Medicine
3 Department of Strategy, Quality & Service Redesign

Austin Health, Heidelberg

Background: CRP is a useful marker of the presence of infection with levels rising during an acute infection and falling with its resolution. It is recommended to be performed no more than three times per week. CRP testing is often performed excessively: either too frequently, or else too many times after it is clear that the infection is responding to antibiotic therapy.

Method: 32 randomly selected patients admitted under the Department of General Medicine during November 2010 who were treated for infection were audited for the number of CRP tests performed during their admission. The number of tests was classed as ‘Less than daily’, ‘Daily’ or ‘More than daily’. Members of the Department of General Medicine subsequently received an education session on appropriate ordering and a second identical audit was performed on General Medical patients admitted during April 2011.

Results: In the first audit, the proportion of patients whose CRP testing was ‘Less than daily’, ‘Daily’ or ‘More than daily’ was 1/32 (3%), 20/32 (63%), and 11/32 (34%), respectively. Following the education program, the results were 23/32 (72%), 7/32 (22%) and 2/32 (6%), respectively.

Conclusion: Education of the General Medical staff was able to reduce substantially the number of excessive orders of CRP tests. As well as ongoing education sessions of new staff, a hospital guideline is being developed and reminders are being built in to CERNER to question whether medical staff require very frequent testing.
HEPATITIS B VIRUS INDUCES LOSS OF CIAP1 AND SENSITIVITY TO TNF-ALPHA IN PRIMARY HEPATOCYTES

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Introduction: Liver damage accompanying HBV infection is largely a host-mediated inflammatory response with activation of apoptosis via the extrinsic pathway by members of the TNF family of cytokines, FasL and TRAIL. Cellular Inhibitor of Apoptosis proteins (cIAPs) are also integral in regulating cell death cellular responses to inflammatory cytokines such as TNF-alpha. In this study, we show that cIAPs are involved in the regulation of HBV replication.

Methods: We used a recombinant adenovirus system to deliver a replication competent HBV genome (rAdHBV) into primary hepatocytes obtained from knock out (ko) mice deficient in intermediates of the apoptosis pathways, cIAP1, cIAP2 and cIAP1/2 double ko and wildtype (wt) mice. Immunoblot analyses were performed to study expression of cIAP and cleaved caspase 3. rAdHBV infected primary murine hepatocytes were assessed for cell viability after incubation with TNF-alpha, FasL and TRAIL. NFkB activity was assessed using a lentiviral NFkB-Luciferase reporter.

Results: Recombinant AdHBV infected murine hepatocytes demonstrated increased caspase-3 cleavage as early as 36h pi that was blocked by treatment with QVD, a pan-caspase inhibitor. Increased caspase-3 cleavage was preceded by a decline in cIAP-1 levels at 24h and the loss of cIAP-1 levels also coincided with sensitization to the cytotoxic action of TNF1, FasL and Etoposide. Induction of NFkB was modest and no changes were seen in other cell death regulation proteins such as TWEAK receptor Fn14, XIAP, TRAF-2 or RIP1. Interestingly, we also show that genetic loss of cIAPs results in increased intracellular levels of HBV DNA.

Conclusions: These results suggest that loss of cIAPs results in death of infected hepatocytes by a cell-autonomous mechanism or by increasing their sensitivity to death ligands. Our data provide genetic evidence that cIAPs are involved in the regulation of HBV infection and replication.

DEREGULATION OF HEPATOCYTE SIGNAL TRANSDUCTION, CIAP1 AND APOPTOSIS BY HEPATITIS C VIRUS.

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Introduction: Hepatitis C virus dysregulates JAK/STAT, ERK and apoptotic pathways. These changes are associated with up-regulation of TGF\(\beta\) and promotion of liver fibrosis. The effect of hepatitis C on the cellular inhibitor of apoptosis protein 1 (cIAP1) has not been previously reported. In this study, we determined the effects of HCV JAK/STAT, ERK, AKT/mTOR and cIAP1 in primary hepatocytes.

Methods: Recombinant adenoviruses expressing HCV genotype 1a CoreE1E2 and NS3 to 5b were used to infect Huh7 cells and primary mouse hepatocytes. Control infections were performed with rAdGFP. Western immunoblots were performed to determine the effects on total and phosphorylated STAT1, STAT3, AKT, mTOR and ERK and total SOCS3. We also investigated the effects on activation of caspase 3, cleaved PARP, cIAP1 expression and oxidative stress.

Results: Infection of hepatocytes with rAdHCV-NS3-5b and rAdHCV-CE1E2/rAdHCV-NS3-5b co-infection produced a 7-fold decline in pSTAT3 levels. A sustained 13-fold increase in SOCS3 expression was observed in coinfectected hepatocytes. Phospho-ERK expression was increased 15- and 30-fold in rAdHCVCoreE1E2 and rAdHCVNS3S5b-infected cells respectively, compared to >100-fold increase in co-infected hepatocytes. Phospho-AKT levels were increased 7 to 12-fold in rAdHCV-CoreE1E2, rAdHCVNS3S5b- and co-infected hepatocytes. Correspondingly, mTOR levels were also increased. Levels of cleaved caspase 3 and PARP were significantly increased and infected hepatocytes were sensitized to the cytotoxic effects of TNF-alpha. This was accompanied by a decline in levels of cIAP1.

Discussion: The expression of HCV structural and non-structural proteins in primary hepatocytes results in dysregulation of ERK, and AKT signalling, down regulation of pSTAT3 and increased SOCS3 and decreased levels of cIAP1 with a concomitant increase in apoptosis. These changes are likely to contribute to liver fibrogenesis.
HEPATITIS C VIRUS-LIKE PARTICLE VACCINES WITH NOVEL ADJUVANTS PRODUCE STRONG NEUTRALISING ANTIBODY AND T CELL IMMUNE RESPONSES IN MHC CLASS I TRANSGENIC MICE

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Background: Clearance of Hepatitis C virus (HCV) requires strong CD4+, CD8+ and neutralising antibody (NAb) responses. Virus like particles (VLPs) resemble mature parent virus inducing protective humoral and cellular immune responses against HCV.

Methods: HCV VLP vaccine was produced in Huh7 liver cells infected with recombinant adenoviruses expressing HCV genotype 1a core-E1-E2 proteins. Mice were immunised with HCV VLPs alone, with alum or two novel lipopetide adjuvants (R4 & E8). Mice were assessed for; (1) humoral responses against VLPs and a recombinant HCV E2 protein, (2) production of Ab secreting cells in splenocytes (B cell ELISPOT assays) (3) Neutralising antibody (NAb) and (4) CD8 T cell responses (IFNγ ELISPOT assay).

Results: HCV VLPs in adjuvants R4 or E8 stimulated the maturation of mouse dendritic cells to levels comparable to lipopolysaccharide (LPS). Strong humoral responses were produced to E2 and VLP in immunised mice. A single dose of vaccine produced high ab titres (VLP/PBS, 3.5Log10; VLP/Alum, 4.1 Log10; VLP/R4, 4.4 Log10 and VLP/E8, 4.8Log10). Strong B cell responses were detected in mice immunized with HCV VLPs in adjuvants R4 and E8 (VLP/PBS, 22; VLP/Alum, 72; VLP/R4, 307; and VLP/E8, 413 Antibody Secreting Cells (ASC)/million splenocytes). Mouse anti-HCV VLP serum neutralized VLP entry into Huh7 cells. The highest NAb responses were mice immunized with HCV VLPs in adjuvants R4 and E8 (80% and 84%). Finally, MHC Class I transgenic mice (produce human HLA class I responses) immunized with HCV VLPs in complete freunds adjuvant, or adjuvant E8 produced strong immediate and memory HCV IFNγ responses.

Conclusion: Mammalian cell derived HCV VLPs stimulate DC maturation, produce strong humoral and T cell immune responses and neutralising antibodies. The immunogenicity of the HCV VLPs was significantly improved by the addition of novel adjuvants R4 and E8. HCV VLPs are a viable vaccine strategy for HCV.

INDUCIBLE RESISTANCE TO CLINDAMYCIN IN STAPHYLOCOCCI: VALIDATION OF VITEK-2 AGAINST CLSI D-TEST

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Background: Clindamycin is commonly utilised in the treatment of Staphylococcus aureus in the penicillin-allergic, or ca-MRSA infection. Inducible resistance to clindamycin is common and termed MLSB (mediated by the erm gene). If an isolate tests resistant to erythromycin but sensitive to clindamycin, it is important to determine if inducible clindamycin resistance is present to avoid reporting false susceptibility as this may lead to treatment failure. The gold-standard method for this is the CLSI D-zone test. The Vitek-2 AST-P612 card contains an ‘inducible clindamycin resistance’ (ICR) test which claims to be accurate; however this has not undergone rigorous independent appraisal.

Methods: Consecutive, non-duplicate, clinical isolates of Staphylococcus spp. resistant (MIC ≥ 8mg/L) or intermediate (MIC 1-4mg/L) to erythromycin were identified. Routine antimicrobial susceptibility testing was performed using Vitek-2, including the ICR test. This was compared against the CLSI-recommended D-zone test using a disk separation of 15mm.

Results: 222 erythromycin-resistant Staphylococci isolates were obtained. Of these, 217 were S. aureus (167 MSSA, 50 MRSA), and 5 were S. epidermidis (4 MRSE, 1 MSSE). Overall 86.5% of isolates were D-test positive. All of the 192 isolates that were ICR positive were confirmed to be D-test positive. Of the 40 ICR negative isolates, 10 of these (25%) were D-test positive and therefore considered false negative results (9 MSSA, 1 MRSA). This correlates with a specificity of 100%, sensitivity of 95%, PPV of 100%, and NPV of 75%.

Conclusions: The ICR test is reliable in the presence of a positive result; however there is a false negative rate of approximately 25%. This will lead to susceptibility reporting errors, with potentially serious clinical implications. A negative ICR should be confirmed by CLSI D-test.
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THIS POSTER IS NON-DIAGNOSTIC: QUALITY ASSURANCE IN COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY

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AIM: Computed tomography pulmonary angiography (CTPA) is a common and clinically critical investigation in suspected pulmonary embolus. High quality scans are essential for diagnosis. This poster presents an audit of factors associated with suboptimal enhancement of the pulmonary trunk (PT) in CTPA. Ethics approval obtained.

METHOD: When performing CTPA, the radiographer places a region of interest (ROI) marker over the PT on a single scan slice prior to contrast injection. At injection, the slice is scanned at one-second intervals, sampling ROI enhancement. When enhancement is sufficient, the complete scan is manually commenced.

100 CTPA studies were retrospectively reviewed and data collected on demographics, radiographic technique and scan quality.

RESULTS: ROI positioning is greatly variable. Only 55% of ROIs were placed as per protocol. Incorrect locations included upstream structures (e.g. superior vena cava), downstream structures (e.g. aortic arch) and soft tissue (e.g. interventricular septum). 7% were performed without a ROI (triggered by ‘best guess’).

Suboptimal enhancement rates were low for ideal ROI positioning (21.8%), high for downstream structures (40%) and highest for 'best guess' methods (71.4%). Patient age under 60 was associated with a suboptimal enhancement rate of 43.9%, compared to 15.3% in patients aged 60 years and above.

CONCLUSIONS: We demonstrate an absolute requirement for accurate anatomical recognition in CTPA radiographic technique. Frequent non-ideal ROI positioning indicates need for ongoing education of radiographers undertaking this technically complex study. The relationship of PT enhancement with patient age suggests a role for unique protocols for patients under 60. This warrants further investigation.

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MENINGIOMA: RADIOLOGIC-PATHOLOGIC CORRELATION

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Aim: - Review false negative and false positive diagnoses of meningioma on MRI reported by Austin radiologists compared with pathology as the gold standard after neurosurgical resection. - Assess accuracy of meningioma diagnosis with MRI. - Identify imaging features which aid correct diagnosis of meningioma. - Identify confounding imaging features that lead to false negative and false positive diagnosis of meningioma. Method: All cases diagnosed with meningioma at imaging or histopathology from the Austin MRI neuropathology audit were assessed for agreement between MRI and histopathology. The data was collected prospectively for all cases with neuropathology and preoperative Austin MRI from 2003. The imaging for all cases of false negative and false positive diagnosis of meningioma was reviewed. Results: The Austin MRI neuropathology audit includes 944 cases since 2003. 97 cases have meningioma as the primary diagnosis on imaging. 98 cases have meningioma proven on histopathology. 6 cases with a MRI diagnosis of meningioma were disproved on histopathology. 7 cases of meningioma on histopathology were misdiagnosed on imaging. Sensitivity 92.9% Specificity 99.3% Review of the imaging revealed a variety of imaging features that help to differentiate meningioma from mimics and highlights unusual imaging appearances of meningioma. Conclusion: Meningiomas are common and it is important that their uncommon appearances and the various mimics are recognized to optimise immediate and long-term management.

CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE: PREDICTIVE VALUE OF Aβ IMAGING WITH 18F-FLORBETaben

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Background: 18F-Florbetaben (FBB) is a novel tracer that has high affinity for Aβ plaques in vitro. [1] It may have a role in the routine clinical work up of individuals with cognitive complaints, to assess for the presence of Alzheimer's Disease (AD) neuropathology in vivo. [2,3]

Objectives: To evaluate FBB retention in elderly mild cognitive impairment (MCI) sufferers and compare it to age-matched healthy controls (HC) and AD participants. To determine the predictive accuracy of FBB for progression of MCI to AD at 18 to 24 months.

Methods: Fifteen HC, 45 MCI, and 15 participants with AD underwent a neuropsychological evaluation, a 3D T1 MRI, and a 20 minute emission scan at 90 minutes after intravenous administration of 300MBq of FBB. Standardized Uptake Value Ratios were calculated using the cerebellar cortex as the reference region. [2] Hippocampal volumes normalised to head size were extracted using statistical parametric mapping. [4] Clinical evaluation of the MCI participants by a neurologist blinded to the baseline imaging results were carried out at 18 to 24 months.

Results: High neocortical FBB binding was seen in 24 (53%) of MCI, compared to 15 (100%) in AD and 3 (20%) in HC. FBB was 87% accurate in predicting progression from MCI to AD at 18 to 24 months. FBB was a better predictor of progression to AD than hippocampal volume.

Conclusion: Aβ imaging using FBB allows earlier prediction of conversion to AD in MCI.

PHANTOM EVALUATION OF PET ATTENUATION CORRECTION USING COMPUTED TOMOGRAPHY IN PRESENCE OF CONTRAST AGENT

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Introduction: Positron Emission Tomography (PET) assesses the quantitative uptake of radiopharmaceuticals and can demonstrate the physiological functions in the body. PET images need to be attenuation corrected (AC) in addition to several other compensations. AC methods such as transmission and transmissionless AC are used to generate AC maps. The conversion of 40-140eV to 511keV photons is different for pixels/tissues that have higher densities resulting in overcorrection in photon attenuation and therefore creating artifacts. Currently there are no algorithms in place that account for the presence of high density mediums such as CT oral or intravenous mediums.

Method: This research project was not performed through the use of humans rather it consisted of Phantoms. The first syringe did not contain any IOSCAN/OMNIPAQUE however consisted of water and a small amount of $^{18}$F-FDG (made up to 50ml). Syringes 2-5 contained 0.25ml, 0.5ml and 1ml of IOSCAN respectively. In regards to the amount of $^{18}$F-FDG(Fluro-Deoxy Glucose) present in syringes 2-4 were kept constant at around 10M bq. A low dose CT and $^{137}$Cs scan was performed followed by a 5minute emission scan. The images were reconstructed using the RAMLA3D iterative algorithm.

Results: From the three IOSCAN studies and the one OMNIPAQUE study, it can be seen that the SUV uptake in both the $^{137}$CsAC and the CTAC is somewhat similar. This indicates that there is no medically significant impact on the presence of IOSCAN nor OMNIPAQUE in relation to both attenuation correction methods.

Discussion: From the results, the phantom preparation is very important. The second set of scans performed resulted in erroneous measurements which results in data that is not valid and cannot be used in this study. When the radioactivity is properly distributed throughout the syringe, the results are of an acceptable value and can be accurately used in the study.


AN AUDIT OF CT BRAIN (CTB) ORDERING WITHIN THE AUSTIN HEALTH EMERGENCY DEPARTMENT

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Objective: To establish the appropriateness of CTB ordering in the ED and compare results to period prior to co-located CT scanner.

Methods: For the period 15/5/10 to 14/5/11, all CTB ordered from ED were extracted from the Medtrak database. 100 random UR were selected and the indications for CTB were obtained. An EP and neuro-radiologist reviewed each case independently. For those cases were there was disagreement, the 2 physicians met and reached consensus. This was the same methodology as 2010 audit. The final CT report was also extracted to determine “yield” – clinically significant abnormalities.

Results: On initial review of indications, both physicians agreed in 78 cases. Of the 22 that required consensus for agreement, most were settled on review of Austin Health Head Injury Guideline. In total 90 cases (90%) were judged to have appropriate indications for CTB.

Increasing use of CTB – In March/April 2010 there were 745 CTB ordered from ED from 11,350 presentations (6.6%). For the same period in 2011 there were 910 scans ordered from 11,942 presentations (7.6%)

Yield – significant intra-cranial abnormalities were noted in 14% of scans, with another 4% having extracranial abnormalities such as facial bone fractures.

Conclusions: The increasing use of CTB does not appear to be driven by convenience – the co-located CT scanner – as the appropriateness of indication on CTB request form remained stable over the two audit periods and remained at an appropriately high level (90%). The appropriate use of CT scan was further supported by a yield figure of 18%.
SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL FLUORO-18 LABELED POSITRON EMISSION TOMOGRAPHY (PET) IMAGING AGENTS FOR HYPOXIC TISSUES IN TUMOURS

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Objectives: To synthesize and investigate the labeling of precursors 1, 2 and 3 via Fluoro-18 exchange using $[^{18}\text{F}]$KF/kryptofix and/or click chemistry using $[^{18}\text{F}]$fluoroethylazide. The potential of these radiolabeled compounds as PET Imaging agents were also evaluated biologically.

Methods: Precursors 1 and 2 were prepared via three steps: firstly, the coupling of (4-nitrophenylthio)aniline with propargyl bromide or 2-ethylbromoacetate to give the corresponding mono-propargyl aniline and mono-ester aniline. These mono anilines were then reacted with 2-chloroethyl triflate to give their respective sulfide anilines. Lastly, the oxidation of the sulfide produced precursors 1 and 2. Precursor 3 was prepared via coupling of aminoazobenzene with 2-chloroethyl triflate. Precursors 1, 2 and 3 were then labeled with $[^{18}\text{F}]$KF/kryptofix at 110°C in DMSO to give hot products 4, 5 and 6. Precursor 1 was also subjected to click chemistry following the procedure described by Glaser and Arstad 1 to give hot product 7.

Results: Synthesis of novel hypoxic imaging agents precursors 1,2 and 3 were achieved with yield of 73%, 43% and 31%. Radiolabeling of precursor 1 via halogen exchange and click chemistry were successful to yield products 4 (15%) and 7 (28%). Biological testing of products 4 and 7 were carried out using Balb/C nude mice bearing SK-RC-52 with a tumour volume of 300 mm$^3$. The preliminary results of the dynamic imaging showed the muscle : tumour uptake ratio of product 4 and 7 was 1:2.5 and 1:1.5 respectively; indicating both compounds have the potential as imaging agents.

Conclusions: The syntheses of precursors 1,2 and 3 have been successful. Radiolabeling experiments of these precursors produced hot products 4, 5, 6 and 7. The preliminary biological studies demonstrated product 4 and 7 as promising hypoxic imaging agents. The radiolabeling of precursors 2 and 3 to give product 6 and 7 are in progress, and in-vivo studies of the corresponding radiolabeled products will be done in impending future.

Research Support: This research was supported by Science Faculty Scholarship, The University of Melbourne, and NHMRC, project grant no. 469002.

BACKGROUND: Determination of radiotracer metabolism is an important part of the evaluation process for new radiopharmaceuticals. Radioactive metabolites can negatively impact on the signal to noise ratio if they show non-specific binding in vivo. Even worse, radioactive metabolites that have affinity for the target can make kinetic modelling difficult and may require extensive blood sampling in order to correct for metabolites.

Since the smooth endoplasmic reticulum of the liver is the principal organ of drug metabolism, in vitro tests using S9 liver fractions or liver microsomes are frequently used in the development of pharmaceuticals. The majority of xenobiotic compounds undergo phase 1 metabolism in the liver, a process that is catalysed by the cytochrome P450 family of enzymes. Phase 1 metabolism is an oxidative process that results in the conversion of a C-H bond into a C-OH bond.

It is usually followed by phase 2 metabolism, where conjugation reactions are catalysed by a variety of enzymes such as the uridine diphosphate glucuronosyltransferases (UGT). The glucuronidated metabolites can be excreted easily since they are highly polar molecules. Unlike the phase 1 metabolites, they normally do not show any affinity for the target.

AIM: The aim of this project was to establish a cytochrome P450 phase 1 metabolism assay in our laboratory and to determine the metabolic profiles and biological half-lives of our novel hypoxia and tumor cell proliferation tracers.

METHODS: The radiotracers were incubated with rat S9 liver fractions, phosphate buffer and either NADPH or an NADPH generating system at 37°C using the CAT Thermo Shaker SH26.3. At the designated time points (30, 60, 90, 120 and 240 minutes) an aliquot was removed and the reaction terminated by the addition of methanol. The reaction mixture was centrifuged and analysed by radio-HPLC. The HPLC system consists of a Shimadzu HPLC controller CBM 20A equipped with a 20 µL injection loop, a SPD-20A UV-Vis detector and two LC-20AD solvent pumps for high pressure mixing of mobile phases. For the detection of radioactive compounds, the Bioscan dual BGO coincidence detector was used.

RESULTS: All novel hypoxia tracers underwent phase 1 metabolism in this assay. The quinone F-18 DS9 had a biological half-life of 22.8 min and at least 8 metabolites could be indentified in the metabolic profile. The nitrophenyl sulfoxide F-18 SO402 had a biological half-life of 43.3 min with only 2 metabolites present. The click chemistry derivative F-18 SO402c had a biological half-life of 32.1 min and only 2 metabolites could be detected. F-18 FMISO did not show any metabolites in this assay.

The proliferation tracers F-18 FLT and F-18 FLETT also showed no phase 1 metabolism. It is known from the literature that FLT only undergoes phase 2 metabolism and this result is therefore consistent with previous observations.

CONCLUSION: We have successfully used a cytochrome P450 assay to model radiotracer metabolism in vitro. The assay allows us to measure the biological half-life of a radiopharmaceutical and we can also determine the metabolic profile. Furthermore, we have access to LCMS and LCMS/MS technology to elucidate the chemical structure of metabolites.
AUTOMATED PRODUCTION OF $^{18}$F 2-FLUOROETHYL AZIDE AND A THYMIDINE ANALOGUE USING THE SYNTHERA MODULE

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Objectives: The aim of this project was to automate the production of the important click chemistry synthon fluoroethyl azide and investigate the subsequent click chemistry reaction with ethynyl deoxy uridine (EDU) in a single pot using the Synthera module.

Methods: An IFP nucleophilic was used for the labelling experiments. 2-Azidoethyl 4-toluenesulfonate (10 µL) in acetonitrile (400 µL) was added to the dried $[^{18}$F]KF/Kryptofix complex. The mixture was then heated to 80°C for 15 min to produce $[^{18}$F]$^1$ EDU (2 mg) and the copper catalyst were added and the reaction mixture was heated to 80°C for 10 min. Acetonitrile was later evaporated at 100°C, followed by the addition of 0.1 N NaOH (4 mL). The reaction mixture was subsequently injected into the HPLC system. The semi-preparative HPLC column used was an Alltech Apollo 5µ C-18 (250 × 10 mm). The following gradient system were employed at a flow rate of 5 mL/min to elute $[^{18}$F]$^2$: 0-8 min 100% 21 mM phosphate buffer, pH 8; 8-20 min: 5% ethanol/21 mM phosphate buffer, pH 8; 20-30 min 10% ethanol/21 mM phosphate buffer, pH 8. The radioactive product peak at 25 min was collected and could be used without further reformulation.

Results: The previously developed manual two-pot distillation method (32%) gave better yields than the one-pot system (15%). The overall synthesis time was reduced by 20 min using the one pot Synthera method. However, the crude reaction mixture of the one-pot method is more difficult to purify and the method is also less reliable due to blockages of transfer lines caused by insoluble copper compounds.

Conclusions: Comparisons of the one-pot Synthera protocol to a manual two-pot distillation method were made for the synthesis of a fluoroethyl triazolyl thymidine analogue. The yield and reliability of the single pot method may be improved by using soluble Cu catalysts. However, due to the difficulty in isolating the tracer from non-radioactive by-products, the distillation method is still the preferred option. The IFP distillation in combination with a second Synthera module may be the ideal solution for the fully automated production of this radiotracer.

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LONG-TERM DRUG SURVIVAL OF ANTI-TNF THERAPY IN ANKYLOSING SPONDYLITIS

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BACKGROUND: Unlike rheumatoid arthritis, the long-term efficacy and safety of TNF inhibitor (TNFi) therapy in ankylosing spondylitis (AS) is largely unknown. METHODS: All biologically-naïve patients with active AS commencing TNFi therapy at a single Center were followed to March 31, 2010. RESULTS: We examined 209 consecutive patients who received a total of 326 TNFi courses for active AS over 581.0 patient-years; the median treatment duration was 32.9 months (range: 0.4-68.3). The first TNFi was infliximab in 87 (41.6%), adalimumab in 66 (31.6%) and etanercept in 56 (26.8%). Men constituted 153 (73.2%) of the study sample and the mean age at inclusion was 42.4 (SD 11.9) years with disease duration of 19.1 (SD 11.3) years. At the close of follow-up, 128 (61.2%) remained on their first TNFi while 52 (24.9%) had switched to their second, and 24 (11.5%) to a third TNFi. The reasons for discontinuation were secondary inefficacy (34.6%), adverse events (24.1%), primary inefficacy (21.1%), convenience (12.0%) and other (8.3%). Treatment discontinuation due to adverse events occurred more commonly for infliximab 19 (17.0%) compared with adalimumab 6 (5.0%) (odds ratio (OR) 3.9, 95CI, 1.4–12.4) and etanercept 7 (7.5%) (OR 2.5, 95CI, 0.9–7.4). Only 13 patients (6.2%) had ceased TNFi therapy entirely (primary inefficacy (3), adverse event (5), planning to conceive (1), other (4)). Drug survival for the first TNFi therapy was 0.82, 0.72, 0.60, 0.53 and 0.43 at 6, 12, 24, 36 and 60 months, respectively. At similar time points, drug survival for the second TNFi was lower only for the first 12 months: 0.74, 0.64, 0.58, 0.52 and 0.44, respectively (p=0.32). For the second course of TNFi, primary inefficacy to the first TNFi was associated with drug survival at 6 months of only 0.50 compared with 0.84 for prior secondary inefficacy and 0.82 for adverse events (p=0.11). Predictors for treatment discontinuation in multivariate analysis were absence of HLA-B27 (hazards ratio (HR) 2.0, 95CI, 1.1–3.8) and female sex (HR 2.0, 95CI, 1.3–3.0). CONCLUSIONS: Switching to an alternative TNFi is common in AS but few patients entirely cease treatment. Primary inefficacy to initial TNFi is associated with low continuation rates of a second TNFi.

BODY MASS INDEX AND LARGE JOINT INVOLVEMENT IN RHEUMATOID ARTHRITIS

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Aim: To examine the relationship between Body Mass Index (BMI) and large joint involvement in Rheumatoid Arthritis (RA) patients. Methods: An observational study of 225 outpatients with RA recruited from a tertiary rheumatology clinic and a private clinic. Large joint involvement was measured by large swollen joint count (LSJC) and large tender joint count (LTJC) from a maximum of 10 joints (wrists, elbows, shoulders, ankles & knees). BMI was divided into quartiles: underweight (BMI < 20), normal (BMI 20–24.9), overweight (BMI 25–29.0), obese (BMI > 30). Multiple variable and logistic regression analysis was performed. Results: Compared to normal weight patients, the LSJC was 0.6 greater in overweight patients (p = 0.03, 95CI 0.0–1.2) and 1.7 greater in obese patients (p < 0.001, 95CI 1.1–2.3). The LTJC was 0.7 greater in the obese group than the normal group (p = 0.03, 95CI 0.0–1.3). 28SJC and 28TJC were not significantly different across different BMI quartiles. Mean DAS28 was 3.0 (SD 1.1) with no significantcant differences between different groups. Excluding the underweight group which had only 11 patients and high mean LSJC and LTJC, logistic regression analysis revealed that LSJC & LTJC increases with BMI quartile with an Odds Ratio (OR) of 1.11 (p = 0.001, 95CI 1.04–1.19) & 1.06 (p = 0.03, 95CI 1.0–1.1) respectively. Age, number of synthetic DMARDs and biologic therapy showed no significant difference between different groups. Excluding the underweight group which had only 11 patients and high mean LSJC, LSJC & LTJC, logistic regression analysis revealed that LSJC & LTJC increases with BMI quartile with an Odds Ratio (OR) of 1.11 (p = 0.001, 95CI 1.04–1.19) & 1.06 (p = 0.03, 95CI 1.0–1.1) respectively. Age, number of synthetic DMARDs and biologic therapy showed no significant difference between LSJC or LTJC. Higher ESR was associated with higher LSJC (OR 1.02, p = 0.04, 95CI 1.00–1.04). Seropositive patients appeared more likely to have a higher LSJC (OR 1.7, p = 0.07, 95CI 0.95–3.06). Females (OR 1.9, p = 0.045, 95CI 1.01–3.08) and prednisolone users (OR 1.8, p = 0.045, 95CI 1.01–3.27) had higher LSJC. Conclusions: Overweight and obese RA patients have greater large joint involvement as measured by LSJC and LTJC compared to those of normal weight. Female sex, seropositivity and prednisolone usage are associated with greater large joint involvement.
IMPROVING MANAGEMENT OF LOW TRAUMA FRACTURES IN A TERTIARY HOSPITAL: THE “FRACTURE CAPTURE” PROJECT

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Follow up after admission for a low trauma fracture is low with a previous audit of the Austin Hospital indicating that less than 1% of in-patients were discharged with treatment related to a fragility fracture, and only 6% had follow up investigation. We aimed to determine if a designated fracture identification and treatment program improved treatment rates following a low trauma fracture. Patients admitted through the emergency department (ED) with a low trauma fracture (hip, spine upper and lower limbs) were identified weekly. Inpatients had clinical assessment and biochemical investigations for secondary causes of osteoporosis. Treatment was commenced according to standardised guidelines. After discharge, endocrine clinic review was scheduled following outpatient DXA and pathology assessments. Patients discharged directly from the ED were contacted via mail to undergo secondary screening. Follow up reminder letters were sent to patients who failed to respond. Over a 24 month period, 955 females (mean age 74.8±11.4 years) and 325 males (mean age 71.1±11.8 years) with fragility fractures were identified. 587 were inpatients (309 hip, 35 wrist, 243 other) and 693 discharged directly from the ED (18 hip, 294 wrist, 381 other). 51% of inpatients were discharged with treatment, compared to < 1% previously and 40% of inpatients underwent assessment and clinic review compared to 6% observed in the prior audit. 53% of those discharged directly from the ED underwent investigations and clinic review compared to no patients prior to the program. 53% of those discharged directly from the ED underwent investigations and clinic review compared to no patients prior to the program. 14% elected to be treated by their own GP or specialist. Of all the low trauma fracture admissions, only 12% potentially went untreated (failed to respond to correspondence). Implementation of a dedicated bone fragility identification and treatment program significantly improved initiation of therapy. Whether this translates into improved compliance and fracture risk reduction required further investigation.

EARLY RETURN TO WORK AND IMPROVED RANGE OF MOTION WITH MODIFIED RELATIVE MOTION SPLINTING (MRMS): A RETROSPECTIVE COMPARISON WITH IMMOBILISATION SPLINTING FOR ZONES V & VI EXTENSOR TENDON REPAIRS.

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Objective: To evaluate the outcomes of modified relative motion splinting compared to immobilisation following repair of extensor tendons in zones V and VI.

Methods: A retrospective analysis compared the outcomes of relative motion splinting with immobilisation. Sixteen patients (16 fingers) were treated by conventional immobilisation splinting for 4 weeks (immobilisation group) followed by mobilisation with avoidance of ‘at-risk/heavy’ activities for a further 4-6 weeks. Twenty-three patients (23 fingers) were treated with the modified relative motion splint (mRMS group) during the day and a resting splint worn overnight for the first 4 weeks. The relative motion splint was continued for ‘at-risk/heavy’ activities for a further 4-6 weeks.

Results: The mRMS group demonstrated statistically significant improvement in range of motion compared with the immobilisation group. This effect was most marked at six weeks (p=0.0194, Two-way mixed ANOVA) with the mRMS group achieving a 12% higher mean %TAM (p=0.0076, Mann-Whitney U Test). Results were similar for both groups 12 weeks post-operatively. Differences in return to work times between groups were statistically significant (p=0.0062, Mann Whitney U test). Average return to work was 9.4 weeks for the immobilisation group and 3.3 weeks for the mRMS group, equating to a 42 day earlier return to work for the mRMS group. There was no incidence of tendon rupture in either group.

Conclusion: This study demonstrates that modified relative motion splintage (finger based without wrist component) can be applied in the post-operative management of single zone V or VI extensor tendon repairs. The main advantages of this protocol, compared to immobilisation include the small simple splint design, and straightforward patient instructions that enables earlier mobilisation, functional hand use, and return to both daily living and work.
A SYSTEMATIC REVIEW OF PARTICIPATION MEASURES POST-STROKE.

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Background: Participation can be severely affected following stroke. Aim: To identify and critically review the measures currently used to assess participation in stroke research. Methods: A systematic review of published articles involving post-stroke assessment of participation was conducted. Relevant articles published between January 2001 and December 2010 were identified through Medline, CINAHL, PsychINFO and ProQuest Central databases. Case studies, cohort studies, and randomised control trials were included. The most frequently used measures were identified and the psychometric properties evaluated. Four independent raters evaluated each measure relative to the International Classification of Functioning, Disability and Health (ICF) Core Set for Stroke (activity and participation categories). Results: Twenty-nine measures were identified. The Stroke Impact Scale (SIS), London Handicap Scale (LHS), Assessment of Life Habits (LIFE-H), Frenchay Activity Index (FAI), Reintegration to Normal Living Index (RNL), and Activity Card Sort (ACS) were used most frequently. No single measure met criteria across all psychometric indices. The SIS, LIFE-H and the ACS covered the widest range of categories on the ICF Core Set for Stroke. Conclusion: This review identified and critically evaluated 6 current and frequently used participation measures and information is provided to guide the selection of participation measures for clinical and research purposes.

SENSE : STUDY OF THE EFFECTIVENESS OF NEUROREHABILITATION ON SENSATION: INDIVIDUAL PATIENT CHARACTERISTICS THAT PREDICT FAVOURABLE OUTCOMES.

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Background: Ability to benefit from rehabilitation may be influenced by individual patient characteristics. Aim and hypotheses: To quantify the impact of individual patient characteristics on ability to benefit from a novel somatosensory discrimination training program. We hypothesised that side of lesion and initial severity of sensory loss would be associated with outcome success, but that prior duration of stroke and age would not. Methods: Fifty stroke survivors with impaired sensation received sensory training within the SENSe randomised control trial. Primary outcome was a combined index of somatosensory discrimination capacity across functional measures of texture discrimination, wrist position sense and tactile object recognition. Impact of individual patient characteristics was investigated using regression analyses. Results: There was no evidence of differences in outcome based on side of lesion, interval between stroke and onset of training, or age. Improvement tended to be larger with milder initial deficit (< -50 standardised-deficit-units) provided the participant was male, or had no prior stroke, or had non-dominant side impairment; but was not statistically significant. Conclusion: Stroke survivors improve following sensory discrimination training, irrespective of side of lesion, time post-stroke and age. Severity of initial deficit may impact, such that those with milder deficits show larger improvement.
SENSCREEN - SENSORY SCREENING STROKE STUDY: DEVELOPMENT AND IMPLEMENTATION OF A STANDARDISED SENSORY SCREENING TOOL FOR USE WITH SUB-ACUTE PATIENTS POST STROKE.

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Background: Many standardised assessments measuring sensory loss developed in research are not yet available for clinical use. A sensory screening tool (SenScreen) has been developed using shortened versions of evidence-based quantitative measures of somatosensation.

Aim: 1) To evaluate the ability of the SenScreen to identify sensory loss in adult stroke survivors with comparable frequency to that of previous data using full test versions and to evaluate the usability, practicality and perceived clinical value of the SenScreen by occupational therapists.

2) In order to include the brief version of the functional Tactile Object Recognition Test (fTORT) as a subtest of the SenScreen, we aim to determine the ability of the brief version of the fTORT to adequately detect impairments in tactile object recognition as compared to the full test version.

Methods: The implementation of the SenScreen will be conducted in three phases: 1. Occupational therapists will complete a pre-implementation survey and undergo training on the administration of the SenScreen. 2. The SenScreen will then be administered on consecutive eligible stroke survivors admitted to two sub-acute rehabilitation settings by trained occupational therapists. 3. A post-implementation survey will be completed by occupational therapists at the end of the trial phase.

Sensitivity and specificity analysis was conducted to determine the validity of the brief 7-item version of the fTORT as compared to the original 14-item version. The implementation of the SenScreen is currently in the data collection phase. Preliminary results of the implementation of the SenScreen will be presented.

THE IMPACT OF FRONTOTEMPORAL LOBAR DEGENERATION ON DRIVER PERFORMANCE.

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Introduction: To date, literature regarding drivers with dementia has primarily focussed on Alzheimer's disease (A.D.). Frontotemporal lobar degeneration (FTLD) is responsible for approximately ten percent of all dementias with the two main presentations causing behavioural change or impairment of language. The most common clinical presnetations are profound alterations in personality and social conduct, with inertia, loss of volition and social disinhibition. A dysexecutive syndrome occurs with deficits in attention, planning, organization, judgement and problem solving. Unlike Alzheimer's disease there is not usually a primary memory disorder.

Objectives: 1. For Occupational Therapy Driver Assessors (O.T.'s) to better understand the driver characteristics of clients with FTLD, how they differ from drivers with A.D.and how the progression of symptoms affects driver performance.

2. To assist O.T.'s in advising other health professionals about the need for driver assessment, the expected rate of decline in driving ability and reassessment timeframes.

Description:

Case studies will be presented, outlining driver characteristics and assessment outcomes, over time.

Contribution to practice: Occupational Therapists play a unique role in assessing and making recommendations regarding individual's licence status. It is important that they are aware of the lesser known impact of dementias, such as FTLD, on driver performance and safety, in order to inform clients, their families and other health professionals.

OCCUPATIONAL THERAPY AND LIVER TRANSPLANTATION: EXPLORING THE SCOPE OF PRACTICE.

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Aim: This paper will describe the potential scope of occupational therapy for adult patients undergoing liver transplantation.

Method: A review of the current available evidence related to occupational therapy and liver transplantation was undertaken. Clinical practice comparisons with other liver transplant units nationally and internationally were also completed to explore current service delivery.

Results: Limited published literature directly linking or discussing occupational therapy and liver disease or transplantation. Clinical practice comparisons showed that the Victorian Liver Transplant Unit is the only adult service within Australia with dedicated occupational therapy as part of their multidisciplinary team. International comparisons covering New Zealand, United Kingdom, Canada and United States again showed a lack of dedicated occupational therapy services.

Conclusions: Austin Health and the Victorian Liver Transplant Unit have recognised and facilitated the contribution of occupational therapy to the quality of life for liver transplant patients. This innovation acknowledges the unique skills of occupational therapists in addressing the functional and occupational performance issues faced by this patient population. Other health facilities would benefit from the introduction and expansion of occupational therapy services into multidisciplinary liver transplant teams. There is also an opportunity for the development of a community of practice with occupational therapists working in other organ transplant teams.

EVIDENCE BASED SUPERVISION,: A BEST PRACTICE MODEL OF SUPERVISION , BASED ON THE VOICE AND INSIGHTS OF OCCUPATIONAL THERAPISTS AND GROUNDED IN EVIDENCE.

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Aim: This poster explores the concept of Evidence Based Supervision, integrating findings from research evidence within the literature and a level 5 quality project.

Method: The formulation of evidence was approached in two ways, through: (1) an exploration of the literature to develop an understanding of the importance of supervision in professional practice and identify components of effective supervision, and (2) a whole of department quality approach to supervision, involving mapping the existing situation and working to identify a preferred model which would incorporate the evidence from the literature and the "lived" experience.

Results: There was a very strong correlation between the findings from the literature and the department based quality project. Supervision supports the development of knowledge in action and the adoption of current research and evidence into practice, facilitating the development, improvement and maintenance of skills and expertise and in turn has the potential to build the body of evidence based on the lived experience of individuals.

Conclusions: Supervision is an investment, promoting health care and professional practice; assisting professionals to work within complex health environments and extending the opportunity to develop professional knowledge and the growth of evidence, based in practice. It was found that supervision needs to be appropriately structured to facilitate optimal benefits.

The importance of the supervisor and supervisee voice is emphasised, in building the body of knowledge around concepts best practice supervision in occupational therapy.
HYPOXIA INDUCIBLE FACTOR 1A (HIF1A) CAUSES POOR RESPONSE TO CHEMOTHERAPY IN ANDROGEN INDEPENDENT PROSTATE CANCERS (AIPC)

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Background: Cancers of the prostate (CaP) are dependent on androgens for growth and thus androgen deprivation therapy is vital for treating patients who are unsuitable for surgery or recurrence post prostatectomy. However, failure of this therapy leads to the development of androgen independent prostate cancer (AIPC), a lethal form of CaP which is refractory to most chemotherapeutic agents. Hypoxia-inducible factor 1α (HIF1α) is a key transcription factor in cell-mediated adaptive response to changes in tissue oxygenation and is over expressed in many human cancers. However, its role in CaP is unclear.

Methods and Results: Western blot analysis was used to demonstrate that HIF1α is overexpressed in AIPC cells (PC3, Du145) as compared to androgen-dependent cells (LnCaP). Cell proliferation assays revealed that the PC3 cells were resistant to destruction by cytotoxic agents including H2O2 (oxidative stress), staurosporine (apoptosis inducer) and 5-fluorouracil (chemotherapeutic drug) as compared to LnCaP cells. Reduction of HIF1α expression in PC3 cells using RNA interference reversed the resistance towards cytotoxic agents and also reduced cell migration (measure of tumour metastasis). Conversely, the hypoxia mimetic cobalt chloride or oxygen deprivation itself (1% O2) induced overexpression of HIF1α in the androgen-dependent cells which increased the resistance to cytotoxic agents. In contrast to the traditional belief that HIF1α concentrations are controlled by post-translational modification and degradation, our data suggest that the increased HIF1α expression in AIPCs is regulated by a ‘GC-rich’ region in the 5’ untranslated region of HIF1α mRNA.

Conclusions: The overexpression of HIF1α may contribute to the refractory nature of AIPCs to most chemotherapy. Targeted HIF1α therapy could increase responsiveness to chemotherapy and better patient survival.

EVALUATION OF AN ONLINE BIOMASS PROBE TO MONITOR CELL GROWTH AND CELL DEATH

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The estimation of cell density and cell viability of mammalian cell lines in cell culture has traditionally been performed using the exclusion dye trypan blue that stains “dead” cells when their cell membrane is damaged. In large scale cell cultures using bioreactors this estimation is performed off-line. The online biomass probe is based on the principle that under the influence of an electric field between two electrodes, ions in suspension migrate toward the electrodes. The cell plasma membrane is non-conductive so that the cells with intact plasma membranes are polarized and act as tiny capacitors and it has been shown that capacitance increases as the cell concentration does. The measurement is based on the linear relationship between the permittivity difference ε1-ε2 and the viable biomass concentration.

This study compares the data obtained using the biomass probe against the cell counts and viability determined by trypan blue exclusion, and also with apoptosis determination measurements using rhodamine-123 and pan-caspase activation by flow cytometry for a number of mammalian cell lines.
OPTIMIZING PHARMACOKINETICS AND TARGETING PROPERTIES OF RECOMBINANT ANTI-LEWIS Y ANTIBODY HU3S193 IN A431 TUMOR-BEARING MICE

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Aim: Previous results have shown that mutations in residues I253, H310 and H435 of the Fc region of human IgG antibodies interfere with the neonatal receptor (FcRn) binding. We have generated an anti-Lewis Y (LeY) antibody, hu3S193, with an alanine mutation (I253A) that shows a shorter half-life than parental hu3S193. The objective of this pilot study was to evaluate 89Zr-labelled hu3S193_I253A as a positron emission tomography (PET) imaging agent.

Methods: Site-directed mutagenesis was performed to generate the hu3S193_I253A heavy chain. Hu3S193_I253A was tested for LeY binding using ELISA, FACS and BIAcore analysis. Parental hu3S193 and hu3S193_I253A were radiolabelled with 89Zr after conjugation to deferroxamine-p-SCN (Df). The 89Zr-Df-labelled antibodies were evaluated in small-animal PET studies at 4, 24, 48, and 72 hours post injection. At 72 hours after injection, animals were sacrificed. Blood samples and organs were collected and counted for radioactivity. Results: Analysis of hu3S193_I253A mutant by ELISA, BIAcore and FACS showed retention of LeY antigen binding. PET imaging demonstrated specific tumor uptake of both 89Zr-Df-labelled parental and hu3S193_I253A at 24 hours post injection and this uptake was maintained for 6 days after injection. Lesions as small as 16 mm³ were clearly detected with both agents. Higher uptake in the liver was detected when using 89Zr-Df-labelled hu3S193_I253A compared to parental hu3S193 (i.e. 15 %ID/g versus 6 %ID/g at 72 hours p.i.). Conclusion: The pilot study of 89Zr-labelled hu3S193 and hu3S193_I253A demonstrated excellent tumor uptake of both agents, with high-contrast images generated of lesions as small as 16mm³. Improvements in 89Zr-radiolabelling chemistry might reduce liver uptake of fast clearing recombinant antibodies.

INNOVATIONS IN SUPPORTIVE CARE PRACTICE: THE BRAIN TUMOUR SUPPORT OFFICER AT AUSTIN HEALTH

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Receiving the diagnosis of a primary malignant brain tumour is a challenging and difficult process for patients and families. Austin Health, in partnership with the John Cummins Memorial Fund, established a dedicated Brain Tumour Support Officer position in 2008 to address some of the supportive care needs of people and families affected by a diagnosis of primary brain tumour. Since the establishment of this unique position, over 100 families have been supported and assisted.

The model of care has been designed to enable patients and families to be supported through their healthcare journey from the point of diagnosis, through to their treatment and beyond. The Brain Tumour Support Officer ensures that patients and family members are given relevant and up to date information regarding their diagnosis, identifies supportive care needs, and makes the appropriate referrals to service providers both within the health network and in the community. Between October 2009 and June 2010, a total of 794 interventions were provided. Interventions included facilitating a monthly support group; individual supportive counselling sessions; family education; referral to specialist providers and over-the-phone contact. During this period, 76% of patients and families accessed the service on at least 2 or more occasions; with 51% of total contacts being face-to-face and 36% telephone support. The most common issues raised were diagnosis, emotional adjustment, carer stress and functional changes.

The Brain Tumour Support Officer is now firmly embedded as part of the Austin Health Wellness and Supportive Care program. The next challenge is to create a sustainable model of support, one that has the potential to extend out beyond the metropolitan health services to reach patients and families in their own communities and help resource the health professionals they access during this difficult and challenging illness.
Nutritional Status, Complementary and Alternative Medicine Use and Nutritional Support of Cancer Patients in Hospice Home Care

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Nutritional Status, Complementary and Alternative Medicine Use and Nutritional Support of Cancer Patients in Hospice Home Care
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Objective: Malnutrition is prevalent in advanced cancer. This study evaluated the relationship between nutritional support and complementary-alternative medicine (CAM) with nutritional status of cancer patients in hospice.

Methods: A cross-sectional study was carried out on 60 patients with advanced cancer in selected hospices in Malaysia. Nutritional status was determined with the Scored Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire. A questionnaire obtained information on nutritional support (oral feeding, enteral tube feeding and parenteral nutrition) and use of CAM (dietary supplements, specific diets, spiritual practices). The relationship between nutritional support and CAM use with nutritional status was examined using Chi-Square testing.

Results: The PG-SGA found 85% of patients to be moderately to severely malnourished; 98.3% received oral feeding with normal diet (67%), soft diet (10%) and fortified products such as Enercal (23%). 1.7% received parenteral nutrition. None received enteral tube feeding. The most common CAM used was multivitamins with mineral (25%), special food supplements e.g. green tea (35.2%) and spiritual practices such as Tai Chi (20%). No significant relationship between nutritional support and nutritional status or between CAM use and nutritional status were detected.

Conclusion: Moderate to severe malnutrition was prevalent in these patients. The main form of nutrition support was oral feeding. The prevalence of CAM use was moderate. Lack of a significant relationship between nutritional support and nutritional status may be the result of a small sample size.

Mechanism of Epithelial-to-Mesenchymal Transition in Metastatic Melanoma

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Background: Melanoma, an aggressive skin cancer, is refractory to current treatment options and the mechanism by which it acquires metastatic potential is poorly understood. We hypothesise that EMT is a crucial mechanism contributing to melanoma progression.

Aim: To investigate whether EMT occurs in melanoma and to identify molecular elicitors, novel markers and signalling pathways regulating EMT.

Methods and Results: Immunofluorescence and qPCR-based EMT gene-expression profiling led to the identification of two subsets of melanoma cell-lines: epithelial-like (E-cadherin high, low N-cadherin), and mesenchymal-like (N-cadherin high, no E-cadherin). These two subsets were represented in each of the patient tumours tested, suggestive of the role of EMT in generating intratumoural heterogeneity.

Epithelial-like cells were sessile, proliferative and drug-sensitive, whereas mesenchymal-like were invasive, less proliferative and drug-resistant. Following exposure to cytotoxic drugs, surviving epithelial-like cells expressed high levels of mesenchymal markers. Thus epithelial-like cells may acquire drug-resistance by undergoing EMT or selection of mesenchymal cells may occur. Microarray-based pathway analysis revealed the activation of the TGF-beta pathway in drug-resistant and invasive melanoma cells. Subsequently, we identified TGF-beta1 as a potent inducer of EMT in melanoma. Gain and loss of function studies of the EMT associated transcription factors led to the attenuation of functions associated with TGF-beta-induced-EMT. These findings demonstrate that TGF-beta 1 dependent activity controls regulatory genes of EMT.

Conclusion: These observations suggest that EMT is an important event controlling phenotypic and functional heterogeneity in melanoma. If this correlates with disease progression, inhibition/reversal of EMT may be a valid therapeutic option in melanoma.
ASSOCIATION OF CT ANTIGEN EXPRESSION AND SURVIVAL IN STAGE III MELANOMA.

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Background: Patients with advanced malignant melanoma (MM) have variable outcomes despite similar stage. Defining prognostic factors is important to identify patients most likely to benefit from novel therapies. Cancer Testis antigens (CTAg) are immunogenic molecules expressed in normal testis and some cancers including MM. We recently reported that in stage II MM, CTAg expression conferred poorer progression free survival (PFS) but not overall survival (OS). Here we investigate stage III and IV patients to determine the prognostic impact of CTAg expression in advanced MM.

Methods: A tissue microarray (TMA) was created from MM tumours resected between 2005-2007, then stained with a panel of antibodies against ten CTAgs. Tumour infiltrating lymphocytes were characterized by CD8, CD4 and FoxP3 staining. T-regulatory (Treg) lymphocyte rates were assessed by CD8:CD4 and CD8:FoxP3 ratios. Results were correlated with clinical parameters.

Results: 62 stage III and 94 stage IV MM were included. In stage III tumours, higher CTAg expression rates, compared with no expression, was significantly associated with improved PFS (median: 69 vs 17mths) \( p=0.02 \), and OS (100 vs 46 mths) \( p=0.038 \). Furthermore, high CD8:Treg rate was associated with improved PFS (82 vs 21 mths). There was no association between CTAg expression and survival seen in stage IV.

Conclusions: In contrast to previously reported findings in stage II MM, CTAg expression was associated with improved PFS and OS in stage III disease. Additionally, high CD8:Treg ratio conferred better outcomes. The clinical impact of emergent spontaneous immunity against CTAg warrants further investigation in patients with advanced MM.

IMRT FOR OROPHARYNGEAL CARCINOMA: IMPROVING ACUTE DYSPHAGIA AND POST TREATMENT WEIGHT MANAGEMENT THROUGH SUPERIOR MIDLINE SPARING DURING DEFINITIVE CHEMO-RADIATION.

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Purpose/Objective(s): Radiotherapy treatment planning plays an integral role in achieving improved clinical outcomes. Radiation can initiate mucosal reactions, resulting in dysphagia and subsequent malnutrition needing supplemental and/or enteral intervention. Weight maintenance post radiotherapy presents a challenge without regular nutritional assessment. Advances in IMRT planning have facilitated improved dose avoidance to midline structures. A correlative study of dosimetry, acute dysphagia and weight management was undertaken to quantify the clinical benefit of this alternate planning method.

Material/Methods: 42 patients with oropharyngeal carcinoma were prospectively analysed in this study. 23 patients were planned using objective based IMRT (XiO (X)), and 19 patients using biological based IMRT (Monaco (M)). All were nutritionally managed. Dose (Dmean and V50Gy) to the larynx was used as a surrogate for midline dose avoidance. Patients were reviewed weekly (weeks 1-7) for acute dysphagia toxicity (CTCAEv3). Weight was assessed weekly and continued post treatment.

Results: Larynx dosimetric sparing was significant with Monaco planning (Dmean: X=49.9Gy, M=41.9Gy, p=0.001; V50Gy: X=49.7%, M=26.5%, p=0.034). Monaco derived plans delivered a significant reduction in acute Grade 3 dysphagia in weeks 5 (X=52.2%, M=18.8%, p=0.035), 6 (X=78.3%, M=27.8%, p=0.001) and 7 (X=100%, M=50%, p=0.001). Baseline weight-loss was comparable at treatment completion (X=5.2%, M=5.7%, p=0.983). Monaco derived plans delivered weight gain at 2-month (X=9.5%, M=6.4%, p=0.049), 4-month (X=12.7%, M=5.8%, p=0.027) and 6-month (X=14.8%, M=0.5%, p=0.013) follow-up.

Conclusion: Treatment induced acute dysphagia may negatively impact quality of life post head-and-neck irradiation. Adequate nutritional support during treatment can facilitate good weight management. When nutritional support is reduced post radiotherapy, together with persisting dysphagia, weight management can be impaired. This correlative study highlights the potential importance of the swallowing mechanism on patient health, and how the utilisation of biological based planning can facilitate improved midline sparing with reduction in resultant toxicities aiding weight management post treatment for improved patient outcomes.
PATHOLOGIC RESPONSES TO GEMCITABINE/PLATINUM-BASED NEOADJUVANT CHEMOTHERAPY FOR MUSCLE-INVASIVE UROTHELIAL BLADDER CANCER

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Background: Neoadjuvant chemotherapy (NC) improves 5% survival in muscle-invasive urothelial bladder cancer (MIUBC). Pathological complete response (pCR), the strongest predictive marker for long term survival, is achieved in 38% and 32% in methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) and cisplatin, methotrexate and vinblastine (CMV) regimens, respectively. A combination of gemcitabine and cisplatin is used in the metastatic setting as it has similar efficacy and better toxicity than MVAC. Carboplatin is sometimes substituted for cisplatin in patients unsuitable for cisplatin but this combination has not been validated. Data for use of gemcitabine and platinum in the neoadjuvant setting are lacking. Aim: To determine the pCR rates of patients receiving NC with gemcitabine and either cisplatin or carboplatin between January 2004 and March 2011 at Austin Health. Methods: Retrospective review of patients with MIUBC (pT2,-T4, any N). Clinical stage at diagnosis and pathological outcome (pathological complete response (pCR), partial response (PR), downstage disease (DS), stable disease (SD) or progressive disease (PD) at cystectomy are recorded. Results: Fifty-five patients were diagnosed with MIUBC. Of these, eight (14.5%) patients received NC. One (12.5%) patient achieved pCR; this patient received carboplatin/gemcitabine. Three (37.5%) patients had disease downstaged, and achieved SD, respectively. One patient had PD. Conclusions: Gemcitabine/platinum combinations are used in Australia but these regimens might lead to lower pCR rates and hence poorer outcomes. Although more toxic, MVAC or CMV should be considered in appropriate patients fit enough to receive them.

EMT IN MELANOMA IS CHARACTERIZED BY UPREGULATION OF TSP-1

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Background: Melanoma is an aggressive skin cancer and no curative treatment exists once progressed into an advanced stage. We recently identified slow-cycling subpopulations within melanoma cell lines which show a gene-expression signature indicative of mesenchymal-like cells and an active EMT process. These mesenchymal-like melanoma cells secret high amounts of Thrombospondin-1 (TSP-1) which act possibly as immune-evasive signal. Objectives: We aim to understand the importance of TSP-1 in melanoma and to identify the underlying mechanisms of its role in EMT and its potential use as a biomarker of aggressive disease. Methods and Results: Microarray analysis of slow-cycling subpopulations within melanoma cell lines identified a gene-expression signature characteristic of EMT. One of the most profound up-regulated genes was TSP-1. Its over-expression in mesenchymal-like cells could be confirmed by qPCR, ELISA and immunofluorescence. Treatment with TGFBeta induced EMT and expression of TSP-1 in epithelial-like melanoma cells. Blocking of TSP-1 by specific antibodies reduced the invasive properties of melanoma cells. And siRNA mediated knockdown of TSP-1 led to the upregulation of E-cadherin besides influencing a variety of other genes. Furthermore, TSP-1 was shown to reduce immune-cell mediated tumour cell killing. Validation of serum-levels of TSP-1 as marker for progressing disease is currently under way. Conclusion: These observations show for the first time that TSP-1 plays an important role as a regulator of EMT in melanoma cells and may be in part responsible for the immune-escape of advanced stage melanomas and their invasive potential.
AN INTENSIFIED CONDITIONING REGIMENT WITH INTRAVENOUS (IV) BUSULPHAN-MELPHALAN (BU-MEL) AND PHARMACOKINETIC (PK) MONITORING PRIOR TO AUTOGRAFTING FOR POOR PROGNOSIS NON-HODGKIN LYMPHOMA (NHL)

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Background: Oral bu-mel conditioning pre-autograft has been used for many years but variability in busulphan gut absorption results in efficacy and toxicity which is unpredictable. IV busulphan has more predictable PK and can be monitored in real-time allowing individualised dose-adjustments. Overseas experience suggests that this regime improves the outcome of chemorefractory lymphoma or myeloma compared with conventional regimens.

Aims: To determine engraftment, transplant-related mortality/morbidity, treatment outcome and effect of PK-monitoring in high-risk NHL patients receiving IV bu-mel. Relevant outcomes were compared with a concurrent cohort of BEAM recipients since 2010.

Method: Eligibility consisted of patients with high-risk NHL: failure to achieve complete remission with induction; chemoresistant or PET-positive post-salvage for relapse; >1 relapse. PK was done on the initial d-7 busulphan dose with results available to make dose adjustments for doses d-5 to d-3, aiming for an AUC of 4500-5000. Repeat PK was performed after the d-5 dose.

Results: 7 patients received bu-mel (M:F 6:1; median age=57) while 14 patients received BEAM (M:F:4:10;median age=40). The estimated weight-based AUC on d-7 PK was less than expected in 6 of 7 patients (median of 9%). Dose adjustment was required in 5 pts and resulted in a higher than expected d-5 AUC in 7 pts (median of 16%).

No patient died within 100 days of transplant. Engraftment was similar in both groups. Morbidities seen more frequently with IV bu-mel were mucositis, culture-positive sepsis and requirement for prolonged opioid infusions, additional anti-emetics, parenteral nutrition, and ICU admissions. Six bu-mel patients remain alive without progression a median of 204 days of follow-up.

Conclusion: While IV bu-mel increases transplant morbidity, early outcomes appear promising in patients with otherwise poor-prognosis lymphoma. PK-monitoring may help ensure appropriate busulphan levels but further refinement of dose-adjustment algorithms is required.

CNS MULTIPLE MYELOMA (MM) – A MULTICENTRE EXPERIENCE OF A RARE MANIFESTATION

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CNS involvement is a rare complication of MM with a dismal prognosis. There is no consensus on treatment and anecdotally, its prevalence appears to be increasing in the era of novel therapy.

Aim: Describe clinical features, treatment response and overall survival (OS) of patients with CNS MM.

Methods: Review of patient records from 1/2000-5/2011 at 4 hospitals identified 17 cases of CNS MM defined by monoclonal plasma cells in CSF and/or radiological evidence of cerebral parenchymal plasmacytoma. A retrospective analysis of clinical and treatment data was performed.

Results: Median age at initial diagnosis was 58 (41-70) years. Seven patients had ISS stage III disease, two presented with extramedullary disease, and 3/10 evaluable had unfavourable cytogenetics. Lambda light-chain restricted cases were predominant (11/17). Patients received a median of 3 prior therapies (1-4); autograft (n=16), allograft (n=2) and at least one of thalidomide (n=14), lenalidomide (n=4) or bortezomib (n=8). Median time to diagnosis of CNS MM was 36 months (1-114). Eight patients had concomitant progressive systemic disease, two were in CR. The most common presentation was cranial nerve palsy (n=7). All patients received combinations of radiotherapy (RT) (n=12), intrathecal (IT) chemotherapy (n=8), systemic chemotherapy (n=3) and/or novel agents (bortezomib n=2, thalidomide n=5).

Median OS from initial diagnosis was 47 (12-124) months. Survival from diagnosis of CNS MM was 4 (1-23) months. IT chemotherapy had superior OS [20 months vs. 2 months (p=0.02)]. There was no improvement in OS for RT (p=0.9). Only 2 patients were alive at time of report (5, 10 months post-CNS MM diagnosis). Both received IT chemotherapy and bortezomib.

Conclusions: Little is reported on the impact of novel agents on CNS MM. IT chemotherapy and bortezomib may be of benefit in selected cases; larger prospective collaborative studies are required to test this observation.
INTERMITTENT GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) MAINTAINS DOSE INTENSITY AFTER ABVD THERAPY COMPLICATED BY NEUTROPENIA

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Introduction: G-CSF is commonly used to maintain dose-intensity in patients receiving ABVD for Hodgkin lymphoma (HL). However, some studies suggest that dose-intensity can be maintained without G-CSF, with minimal incidence of febrile neutropenia. Moreover, G-CSF is expensive (approximately A$1925 for pegfilgrastim and A$1050 for 7 days of 300ug filgrastim per cycle) and is associated with side-effects including bone pain and increased risk of bleomycin-related lung toxicity. Intermittent G-CSF may be an effective compromise, given that G-CSF effect on granulocyte precursors in-vitro persists for 4-5 days after administration and intermittent scheduling is effective in maintaining dose-intensity in breast cancer patients receiving adjuvant chemotherapy. After a promising pilot study using intermittent G-CSF for ABVD complicated by neutropenia, this schedule has been used at physician discretion at RMH.

Aims: To compare the efficacy of daily/pegylated versus intermittent G-CSF protocols between 1996 and 2009.

Methods: Retrospective analysis of the incidence of neutropenia, treatment delays and febrile neutropenia in patients receiving different G-CSF schedules.

Results: 848 cycles in 85 patients (M:F 43:42; median age = 32 (range:14-71) years) with predominantly stage II/III HL were evaluated. The median neutrophil count when cycle 1B was due was 0.9 (range:0-18.7). Most patients(86%) received G-CSF, generally commencing during cycle 1B. Intermittent G-CSF (typically given on days 4,8,12) was used in 452 cycles compared with 99 cycles for daily/pegylated G-CSF. Febrile neutropenia occurred in 2 and 0 cycles respectively and no treatment delays due to neutropenia occured in either group. After intermittent G-CSF, the median neutrophil count was 7.3 (range:1.4-47.1x10⁹/L) when chemotherapy was next due, similar to other G-CSF regimens. The cost difference between pegfilgrastim and three doses of 300ug filgrastim per cycle over 11 cycles (i.e. cycles 1B-6B) was A$16500.

Conclusions: Intermittent G-CSF is effective in maintaining dose-intensity in patients receiving ABVD, resulting in substantial cost savings.

HIGH-DOSE METHOTREXATE FOR THE TREATMENT OF RELAPSED CENTRAL NERVOUS SYSTEM (CNS) ERDHEIM CHESTER DISEASE (ECD)

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Introduction Erdheim-Chester disease (ECD) is a rare non-Langerhan's histiocytosis with multi-system involvement including CNS disease which confers a poorer prognosis. There is no definitive treatment for ECD, though interferon-alpha may be useful for non-CNS disease, if given for more than 3 months.

Case Report

A 60-year old lady with a 5-year history of stable non-CNS ECD presents with 4 days of diplopia and right arm numbness. Neurological examination revealed a horizontal gaze palsy and right arm paraesthesia. Her MRI brain showed an extensive brainstem/cerebellar lesion but her PET/CT scan revealed stable systemic disease. CSF analysis showed raised protein (3.12g/L) but no evidence of infection or malignancy. A brain biopsy was not performed due to the risk of permanent neurological damage and a presumptive diagnosis of CNS relapse of ECD was made. During the first 72-hour period, our patient rapidly developed dysarthria and ataxia, rendering her bed-bound. This necessitated urgent treatment, but interferon-alpha was not ideal due to its slow onset of action and poor CNS penetration.

We chose high-dose methotrexate (8g/m²), due to its excellent CNS penetration and known therapeutic effect on CNS lymphoma. This treatment arrested the rapid progression and led to a significant improvement in her speech and ataxia. A post-induction MRI brain showed a reduction in the size of her brainstem/cerebellar lesion and her CSF protein reduced to 0.53g/L.

She remained stable with ongoing high-dose methotrexate for 4 months, but subsequently developed new right-sided weakness and an increase in the size of her brainstem lesion. She is currently being treated with interferon-alpha.

Conclusions: We describe a case of CNS relapse of ECD in the setting of well controlled systemic disease. High-dose methotrexate was an effective initial salvage agent but further systemic treatment (e.g. interferon-alpha) may be necessary for a sustained long-term response.
FOXP3 OVEREXPRESS INHIBITS GROWTH OF MELANOMA CELLS IN VITRO
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FOXP3 is a transcription factor originally identified as master regulator of the immunosuppressive functions in CD25+ regulatory T cells (Treg). However, some cancers including melanoma and pancreatic adenocarcinoma also express FOXP3. Furthermore, FOXP3-expressing pancreatic cancer cells inhibit T cell proliferation, suggesting a role for FOXP3 in immune evasion in pancreatic cancer. In contrast, FOXP3 expression is downregulated in breast and prostate cancers compared to normal adjacent tissue. Mutations in FOXP3 have been identified in these tumours, and FOXP3 has been shown to deregulate expression of key oncogenes in breast and prostate cell lines, suggesting a tumour suppressor role. The aim of the current study was to investigate the function of FOXP3 in melanoma. A FOXP3 expression vector or control vector was transfected into FOXP3 negative SK-MEL-28 melanoma cells and multiple FOXP3 positive and vector only clones were selected. FOXP3 overexpression was confirmed by FACs and the growth of the lines was characterized using multiple assays. Microarray profiling was performed to identify gene expression differences. FOXP3 overexpressing clones demonstrated significantly slower growth rates compared to control as assessed by MTS assay, cell number, clonogenicity and growth in soft agar. We are currently analysing our microarray data to identify FOXP3 target genes. FOXP3 overexpression significantly reduces the growth of melanoma cells suggesting FOXP3 is a tumour suppressor in this tumour type, as recently indicated for breast and prostate cancer. The gene expression changes driving this process, and whether FOXP3 also plays a role in immune evasion in melanoma is currently being evaluated.

GENERATION OF A MELANOMA RESOURCE DATABASE
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Australia has the highest rate of melanoma in the world. The rapid increase in incidence and the high mortality have motivated efforts to define the factors driving melanoma genesis and progression. However, one of the main challenges is that melanoma is remarkably heterogeneous resulting in considerable controversy within literature. The aim of this project is to establish a unique resource for melanoma research by acquiring gene-expression profiles, exon-sequencing data and miRNA profiles of over 60 melanoma cell lines established at the LICR, Austin-Melbourne Branch.

We established more than 60 melanoma cell lines from patient tumours and all lines were HLA-typed to confirm their origins. To address temporal changes in gene-expression and to take into account the different levels of gene regulation, RNA, genomic DNA, miRNA, cell blocks for the assessment of intra cell line heterogeneity by IHC, and protein lysates for the confirmation of expression data were generated at the same passage. Establishing this unique melanoma resource database enables us to create genome-scale models to categorize cell lines and subsequently patients into different subgroups leading to informed designs of preclinical in vitro experiments and clinical trials.
INTRACTION PROSTATE MOVEMENT AND THE ZERO ACTION THRESHOLD

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In September 2009, a zero action threshold was implemented for online correction image verification. For prostate cancer patients with gold fiducial markers in situ, an in-field image was captured on every treatment field, daily. An Austin Health Ethics approved retrospective analysis of the images captured between September 2009 and September 2010 for this patient cohort was performed. This study analyses the impact on the accuracy of treatment delivery when reducing from a 3mm to 0mm action threshold for prostate cancer patients.

58 prostate cancer patients treated between September 2009 and September 2010 were identified. The patients were treated with Intensity Modulated Radiation Therapy or Three-Dimensional Conformal Radiation Therapy.

The in-field (offline) images were independently reviewed by one investigator (SG) for verification of the original match performed. The mismatch data was exported into an Excel™ spreadsheet and de-identified. By comparing the mismatch data from each subsequent treatment field for each fraction, the intrafraction movement of the prostate was determined.

Analysis indicates that a zero action threshold online correction policy is a valid, efficient and accurate approach. Intrafraction movement of the prostate is observed on all patients but the magnitude is patient specific.

Intrafraction movement of the prostate will occur, however this does not preclude the use of a zero action threshold online correction policy. The 58 patients analysed in this retrospective study has shown that the intrafraction movement can be patient specific and that the use of the zero action threshold improves the accuracy of the treatment delivered.

SUSTAINED IE GENE INDUCTION IS LINKED TO HDACI-INDUCED APOPTOSIS IN MULTIPLE TUMOUR TYPES

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Background/Aim: Histone deacetylase inhibitors (HDACi) are a novel class of cancer therapeutics currently approved for treatment of cutaneous T-cell lymphoma (CTCL). We have recently established that the drug sensitivity of colorectal cancer (CRC) cells to HDACi is linked to the induction of multiple immediate-early (IE) genes. The study aim was to investigate whether these findings are applicable to other tumour types and to elucidate the mechanism of apoptosis induction involving IE genes. Methods: Drug sensitivity was determined for 40 cancer cell lines, including that of CTCL, multiple myeloma, NSCLC, melanoma, breast and prostate cancer. Apoptosis response was determined at 72 hr post drug treatment (EC50 dose) by measuring the sub-G1 populations in PI/FACS analysis. Quantitative RT-PCR was performed to determine gene expression changes upon drug treatment. RNAi-mediated knockdown of target genes was performed by transient transfection of siRNAs into cancer cells using Lipofectamine. Results: Expression of six IE genes (Fos, Jun, Atf3, Egr1, Egr3, Gadd45b) were preferentially induced by HDACi treatment in sensitive cancer cell lines and the level of IE gene induction positively correlates with apoptosis induction. HDACi-induced IE gene expression is prolonged and sustained over 24 hr; whereas growth stimuli such as EGF and PMA induced IE genes in a rapid and transient manner, peaked at 2 hr. Down-regulation of Jun and Atf3 partially blocked HDACi-induced apoptosis. Conclusions: Sustained induction of IE genes is a consistent transcriptional response induced by HDAC inhibitors in multiple tumour types. AP-1 transcription factors, Jun and Atf3, are functionally involved in apoptosis induction.
INTRODUCTION

In patients undergoing cardiac surgery, pre-operative anaemia has been shown to predict post-operative transfusion requirements and to be an independent mortality risk factor. A preoperative haematinic screen was trialed to identify reversible causes of anaemia pre-operatively.

METHOD

150 patients attending an anaesthetics review for planned cardiac surgery underwent a haematinic screen. Anaemia was defined as a haemoglobin below 115g/l in females and below 130g/l in males. Iron deficiency was defined as a ferritin below 11 µg/l in females and below 24 µg/l in males in the absence of raised inflammatory markers CRP and ESR. Intervention was implemented where possible to correct iron deficiency with or without anaemia. Intra-operative and post-operative transfusion data was completed for 92% of patients over a 12 month period from July 2010 to July 2011.

RESULTS

Table one: incidence of iron deficiency and anaemia by gender and post-operative red cell transfusion rate for each parameter.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Iron deficiency</th>
<th>Anaemia</th>
<th>Post operative rate of transfusion of red cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td></td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Male</td>
<td>5%</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td>Female</td>
<td>6%</td>
<td>18%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Conclusions: The low rate of iron deficiency identified in this population of patients undergoing cardiac surgery has not provided evidence to recommend a haematinic screen as a pre-operative tool. In addition, although iron deficiency was predictive of post-operative red cell transfusion in women, the same association was not seen in men. Pre-operative anaemia remains a strong indication for transfusion, reflecting this mult factorial contribution to morbidity and mortality in cardiac surgery.
COMPLEX PROTEIN INTERACTION NETWORKS OF CD151-PROMOTED CELL MOTILITY AND METASTASIS IN PROSTATE CANCER: A SYSTEMS BIOLOGY ANALYSIS

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Prostate cancer (PCa) is one of the leading causes of cancer death in men. Previous studies from our laboratory revealed that expression of the tetraspanin CD151 is different amongst different histological grades of PCa and high levels of expression are linked to shorter survival¹. In vitro motility assays of human PCa cell lines suggest CD151 is a motility and metastasis promoter². Our aim is currently to focus on a systems biology approach by examining protein-protein interaction networks involved with CD151.

We have analyzed a set of microarray expression data from PCa cell lines PC-3 and CD151 knock-down PC-3 (KD PC-3) cell lines, and identified differentially expressed genes. One hundred and seventy two genes were found to be significantly associated with changes in CD151 expression in PC-3 cells which were affected as a result of knocking down CD151 expression. While mechanisms underlying CD151-promoted cancer cell motility are still largely unknown, identification of interaction networks may lead to better understanding of cellular processes. We examined the protein interaction networks of our differentially expressed genes using Cytoscape³. We have identified extended biological networks, which are modules of interconnected proteins which share functional connectivity based on known functional annotations and molecular interactions. Functional network analysis revealed high level of connectivity surrounding genes involving in transcriptional regulation, microtubule-based movement and protein folding and complex formation.

A systems biology approach allows for improved mechanistic interpretation of biological data and may facilitate identification of therapeutic targets for prostate cancer.

KI67 EXPRESSION IN OESTROGEN RECEPTOR POSITIVE BREAST DUCTAL CARCINOMA

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Aims Gene expression profiling classifies ER positive breast cancer into two main subtypes[1]. Luminal A tumours have a better prognosis than luminal B tumours, are tamoxifen sensitive and derive less benefit from adjuvant chemotherapy. A high Ki67 proliferation index (>14%) has been proposed as a cost-effective means to distinguish luminal B from luminal A tumours[2]. We aimed to assess the reproducibility of classifying ductal carcinomas into luminal subtypes by Ki67 expression using manual scoring and image analysis.

Method: Immunohistochemistry for Ki67 was performed on ninety ER positive invasive ductal breast carcinomas diagnosed at Austin Pathology. The Ki67 index was assessed semi-quantitatively by two pathologists and quantitatively by image analysis using Aperio digital scanning system. Correlation between scoring methodologies and BRE grade were assessed.

Results: Preliminary results show a correlation between high Ki67 index and high BRE grade. Manual Ki67 index scoring and Aperio image analysis scoring results were well correlated, but indicate a differing proportion of tumours exceeding the 14% cut-point.

Discussion: Most ductal carcinomas were classifiable as Ki67-low or Ki-67 high by either technique, though different methods may require validation of differing cut-points. The heterogeneous distribution of Ki67 expression can limit the precision of quantitative measurement.

Presenting author statement of original idea and contribution: Experimental design including image analysis methodology, tumour review and block selection, assessment of manual and Aperio image analysis Ki67 scores, data analysis.

References
DIAGNOSIS AND MANAGEMENT OF ACQUIRED HAEMOPHILIA A IN A MAJOR TEACHING HOSPITAL IN MELBOURNE, AUSTRALIA: REVIEW OF 5 CASES.

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Acquired autoantibodies against factor VIII is a rare but potentially fatal bleeding disorder with an incidence of around 1.5 per million people.

Clinical presentation is often large haematomas and/or extensive ecchymoses in the context of a prolonged APTT. Spontaneous haemarthrosis seen in congenital haemophilia A is generally not a feature. Post surgical bleeding complications can be the initial presentation. Risk factors are not identified in the majority of cases however older age, pregnancy and autoimmune disorders are often reported. Diagnosis requires clinical acumen to raise suspicion to support systematic and proficient laboratory procedures. The principles of management are the use of bypassing agents to manage acute bleeding in conjunction with longer term immunosuppression, with an aim of complete inhibitor eradication.

We present 5 case studies of acquired inhibitors against factor VIII, a group of 3 elderly patients above 80 years (1 male and 2 female), a 54 year old male and a 22 year old post partum female. Excluding the post partum female all patients presented with large haematomas and/or ecchymoses with a prolonged APTT. One elderly patient experienced post operative bleeding complications. Diagnosis was confirmed with The Bethesda assay. One elderly female was not treated and died of an unrelated medical condition. The remaining 4 patients received recombinant activated factor VII (rFVIIa) and immunosuppressive therapy. Immunosuppressive therapy including management of relapse required individual adaptation.

The diagnostic and management complexities of acquired haemophilia A and the phenomenon of an infrequently observed clinical scenario provide many challenges. In this heterogeneous condition development of treatment algorithms with the aim of broad application may not provide the best outcomes. Rather rapid control of bleeding and adequate inhibitor eradication in the context of each individual patient's clinical presentation should remain the prime goal.

EPIGENETIC MODULATION OF TUMOUR TARGETS FOR ENHANCED IMMUNOTHERAPY OF CANCER

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The past 12 months have seen immunotherapy for the treatment of cancer progress from a promising research field to established therapy with the approval of clinical therapies Ipilumumab and Sipuleucel-T for advanced disease. Successful clinical outcomes for therapeutic cancer vaccines will depend on the generation of robust immunity and the expression-profile of the target antigens. Although the most immunogenic of tumour antigens, the family of cancer-testis antigens (CT-Ag) are frequently heterogeneously expressed within solid cancers with their expression controlled through a process of epigenetic regulation. If the tumour expression of members of this antigen family could be enhanced, then a greater proportion of tumour cells would be susceptible to immune-mediated killing. In this study we examined in vitro whether the demethylating agent 5-aza-2'-deoxycytidine increases expression levels and the percentage of cells expressing members of the CT-Ag and the effect this mediates on recognition by killer T cells. Using quantitative PCR we demonstrated upregulation of messenger RNA and by immunohistochemistry showed increase in protein expression in treated melanoma cells. However, heterogeneous expression of the antigens was maintained. Using specific killer T cells we observed that although antigen levels increase, no consistent increase in immune-mediated killing is observed. A number of published studies have proposed epigenetic modulation in order to enhance immunotherapy. Our data suggest that although an increase in antigen expression may be achieved, due to potential broad expression changes in many additional genes and inherent heterogeneity in cancer, the approach may not be successful clinically but warrants further investigation.

† AB and AK contributed equally.
A SURVEY OF TAXOTERE-CYCLOPHOSPHAMIDE-HERCEPTIN (TCYCH) CHEMOTHERAPY USE AND SAFETY PROFILE IN HER-2 POSITIVE BREAST CANCER PATIENTS IN AUSTRALIA

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Aim: Following the positive results in early breast cancer studies, PBS states that funded trastuzumab must be used concurrently with chemotherapy in this setting. Alternative nonanthracycline regimens which are better tolerated with comparable benefit have been sought for use in "low risk" Her-2 positive patients. Taxotere-Cyclophosphamide (TCyc) treatment was associated with improved overall survival compared with doxorubicin-cyclophosphamide in non-Her2 selected groups. There is limited data however in using TCyc in combination with trastuzumab. The extent of use of TCycH in Australia is unknown. The aim of the study is to review its use and safety amongst Australian oncologists.

Methods: An online survey collected information on oncologists' experience with TCycH. Those who used this regimen submitted case data on patient and tumour characteristics, and toxicities experienced. Non-prescribers were given scenarios to survey use of alternative regimens.

Results: Preliminary data was collected from 26 sites. For non-prescribers, the reason given was a perceived lack of efficacy data. In 66 TCycH cases, there were 69.7% Stage I, 72.7% T1a-c and 83.4% node negative tumours. All were Gr2/3. Over 66% were hormone receptor positive. Only 30.5% had pre-existing cardiovascular disease. 4 patients had EF <50% during treatment with 5 developing NYHA G1/2 CCF. 37 patients experienced G3/4 neutropenia with 50.8% completing treatment without G-CSF support and only 25% febrile neutropenia rate.

Conclusion: TCycH is a well tolerated chemotherapy regimen with low risk of cardiac and myelotoxicity. It has been primarily used in Stage 1, node negative and hormone receptor positive "lower-risk" Her-2 positive breast cancers amongst Australian oncologists.

THE EFFECT OF MICROENVIRONMENTAL FACTORS ON THE BIOLOGY OF PRIMARY PROSTATE CANCER CELLS IN VITRO

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Introduction: Prostate cancer (PC) affects 13,000 Australian males annually and once metastasised, the most common site being bone, is incurable. Novel treatment strategies are required as current models of PC are limited to a small number of cell lines and animal models that don't recapitulate the human disease. This study aimed to examine the biology of primary PC cells in response to defined microenvironmental factors that are found within the prostate and/or the bone.

Materials and Methods: Primary PC epithelial cells were isolated from radical prostatectomy specimens using enzymatic digestion and EpCAM-mediated bead purification, and cultured in defined epithelial growth medium. The biological properties examined were: 1) adhesion to extracellular matrix proteins; 2) proliferation on extracellular matrix proteins; and 3) proliferation in response to exogenous factors.

Results: Primary PC epithelial cells bound to collagen I and Matrigel but not laminin or osteopontin. Immediately following isolation, they proliferated best on laminin, however this was not seen after passaging. Treatment with conditioned medium from cancer-associated fibroblasts and osteoblasts stimulated proliferation, while treatment with androgen, EGF, FGFs, or HGF alone had no effect. TGFβ and TNFα inhibited proliferation without affecting apoptosis.

Conclusions: The biology of primary PC epithelial cells is affected by specific soluble and extracellular matrix factors. While the more complex conditioned medium preparations gave significant responses, a number of individual cytokines had no effect on PC proliferation, possibly due to loss of receptors during culture, or lack of permissive factors. Current studies are aimed at further understanding these effects.
CHARACTERISATION OF PRIMARY PROSTATE CANCER CELLS IN VITRO
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Introduction
Prostate cancer (PC) affects 13,000 Australian males annually, and is incurable once it has metastasised. Current models of PC are limited to a small number of cell lines and animal models that don't recapitulate the human disease. Primary PC cells can be cultured in vitro for ~6 weeks and offer a model that is closer to the human disease. The aim of this study was to characterise cultured primary PC cells.

Methods: Primary PC cells were isolated from radical prostatectomy specimens using enzymatic digestion and EpCAM bead purification, and cultured in defined epithelial growth medium. The proportion of the two main prostate epithelium cell types, luminal (cytokeratin 18-positive) and basal (cytokeratin 5-positive) cells was assessed using flow cytometry and immunocytochemistry immediately after isolation and after passaging in culture. Receptor expression for PC microenvironmental cytokines was also examined.

Results: Following isolation, primary PC cells were ~50% luminal and 50% basal cells. They expressed receptors for androgen, EGF, FGF, HGF, TNFα, and TGFβ. With progressive culture, the proportion of basal cells increased to >80%, while luminal cells decreased to <20%. Androgen receptor (AR) expression decreased significantly with time in culture. Other receptors were unchanged.

Conclusions: As expected, the culture environment plays a significant role in the growth of primary PC cells. Our current culture conditions appear to maintain basal (CK5-positive) rather than luminal (CK18-positive) cells; thus data generated using this culture system must be interpreted with this in mind. This can also explain the apparent loss of AR expression, as basal cells do not express AR.

CONTROVERSIES IN THE MANAGEMENT OF MALIGNANT PLEURAL MESOTHELIOMA: THE CASE FOR CONSERVATIVE SURGERY AND HIGH-DOSE HEMITHORACIC RADIOTHERAPY
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Background: Mesothelioma is a malignancy with high mortality where locoregional progression is the overwhelming cause of morbidity and death. Hemithoracic radiotherapy is regarded by most institutions as unsafe unless the lung has been resected. Extrapleural pneumonectomy is rarely performed and multimodality treatment programs must balance the potential risk of major toxicity with palliative benefits.

Methods: We have delivered high dose intensity-modulated radiotherapy (IMRT) to the whole hemithorax in patients with good performance status and incompletely resected localised disease. All had PET/CT scans to exclude distant metastases, define residual gross tumour volume (GTV), quantify metabolic responses by serial total glycolytic volume (TGV) analysis, and assess locoregional control.

Results: From July 2007 to June 2011, 23 patients with incompletely-resected mesotheliomas received IMRT to the whole hemithorax to 55 - 60 Gy, all at the Austin. 80% had advanced clinical stage and only one patient had a pneumonectomy. IMRT was well tolerated, with no grade 4-5 radiation toxicities. Assessable TGVs were reduced to 40% post-irradiation. Median followup was 8 months (range 2 to 44 months) and 13 patients remain alive, 8 disease-free. Relapses have occurred outside the GTV in 11, including only 3 with concurrent in-field relapse, a locoregional control rate of 85%.

Conclusion: Mesothelioma is radiosensitive and durable local control can be achieved. Advanced radiation technologies, including IMRT and IGRT, allows adequate sparing of adjacent normal tissues. Complete macroscopic resection is no longer mandatory and radical diaphragmatic and pericardial reconstructions, together with mediastinal lymphadenectomy, can be avoided since sophisticated radiotherapy can sterilize gross residual disease without producing significant pulmonary, hepatic or cardiac toxicity, even in patients who retain the affected lung. These techniques can be safely delivered to selected patients following suboptimal surgery and chemotherapy and are recommended to provide palliation and locoregional control to patients with advanced mesothelioma.
CHARACTERISATION OF IMMUNE INFILTRATES IN MALIGNANT AND BENIGN PROSTATE TISSUES

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Aims: To evaluate and compare the proportion of T regulatory (Treg) and activated CD8+ T cells found in prostate cancer (PC), benign prostatic hyperplasia (BPH) and normal prostate tissues (NP).

Methods: Fresh PC, BPH and NP tissues collected from patients were digested and tissue infiltrating lymphocytes were studied as single cell suspensions. Patients’ matching peripheral blood was collected and peripheral blood mononuclear cells (PBMC) were isolated using Ficoll separation. Tissues and PBMC were stained for surface antigens CD3, CD4, CD8, CD25, CD45, CD69 and intracellular antigen FoxP3. Using flow-cytometry, Treg (CD45, CD3, CD4, CD25 and FoxP3 positive) and activated CD8+ T cells (CD45, CD8, CD69 positive) were identified. The proportions of Treg and activated CD8+ cells in PC, BPH and NP tissues were then compared with each other and with their matching PBMC. CD8+:Treg ratio was derived as a measure of in-situ immune-suppression; a low ratio implies an immunosuppressive environment.

Results: Prostate tissue samples and matching PBMC have been collected from 32 patients. We present data for 20 patients (10 PC, 4 BPH, 4 NP). From our preliminary data, the CD8+:Treg ratio in BPH, NP, and PC tissues was 176, 371 and 116 respectively. The percentage of CD8+ cells in prostate tissues were: BPH 1.59%; NP 1.64%; PC 1.42%. The percentage of activated CD8+ cells: BPH 79.14%; NP 71.49%; PC 69.17%. Statistical analyses and complete data will be presented.

Conclusions: These preliminary data imply relative intratumoural immunosuppression in PC tissue compared with BPH and NP. This suggests that local immunosuppression might play an important role in prostate cancer oncogenesis or persistence.

SCREENING FOR SUPPORTIVE CARE NEEDS AT COMMENCEMENT OF CANCER TREATMENT

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Aim: To implement a sustainable process for routine validated screening for the supportive care needs of patients commencing chemotherapy and radiation therapy.

Method
Clinicians and consumers evaluated available screening tools. Action and referral pathways identified to address needs raised. Multidisciplinary team of staff trained. Supportive care screening implemented at commencement of cancer treatment in day oncology, radiation oncology and cancer wards for 16-week pilot period.

Results: 220 patients were screened using the patient-administered NCCN Distress Thermometer (DT). A significant number of patients (38%) indicated moderate to severe distress (scores ≥ 4), with the majority of patients (62%) indicating mild distress (scores < 4). Patients on the Wards indicated more distress (4.0) than patients in Day Oncology (3.3) or Radiation Oncology (2.6). Most problems indicated were from the physical (50%) and emotional (41%) domains. A referral for further supportive care follow-up was offered to 41% of screened patients, and accepted by 30% patients screened.

Discussion
Training of multidisciplinary staff enabled successful incorporation of screening into routine patient care. Most clinicians reported that it improved rapport with patients, and allowed identification of problems possibly not otherwise detected. Most patients surveyed reported the DT helped communicate their needs with staff, appreciated the opportunity to discuss issues, and would be happy to repeat the screening.

Implications for Practice
Local demonstration of successful screening warrants efforts to sustain the screening model used and expand it to include all cancer patients admitted to the oncology wards and palliative care unit. Repeat screening points will also be introduced.

(1) Department of Human Services (DHS), 2009, Providing optimal cancer care, Supportive care policy
(2) National Breast Cancer Centre (NBCC) and the National Cancer Control Initiative (NCCI), 2003,
TUMOUR TARGETING OF THE ANTI-EPHA3 ANTIBODY, CHIIIA4, REDUCES TUMOUR BURDEN AND EFFECTS VASCULATURE OF HUMAN PROSTATE CANCER TUMOUR XENOGRAFTS

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Eph receptor tyrosine kinases (Ephs) and their membrane bound ephrin ligands (ephrins) control cell positioning and tissue organisation. Their de-regulated re-emergence in adults contributes to tumour invasion, metastasis and neo-angiogenesis. Due to over-expression in a wide variety of human tumours there is increasing interest in Ephs and ephrins as targets for anti-cancer therapies. In particular, large-scale screens for frequent somatic mutations in tumour patients emphasise EphA3 as a candidate cancer gene and our analysis of a variety of human tumour sections by immunohistochemistry reveals EphA3 expression, not only in the tumour cells but in the stroma as well, both in the mesenchymal cells and in some cases the vasculature.

We have previously shown that the mIIIA4 monoclonal antibody, specific for native EphA3, efficiently targets EphA3 positive human tumour xenografts. We now demonstrate that the human/mouse chimeric agonistic anti-EphA3 antibody, chIIIA4, inhibits tumour growth by disrupting tumour stroma and neo-vasculature. Furthermore, we have utilized intravital multiphoton microscopy to monitor quantum dot-labelled chIIIA4 targeting in vivo, thereby allowing us to directly visualise expression of EphA3 on tumour vasculature as well as monitoring disruption of the tumour vasculature and dispersion of the stromal tumour capsule in chIIIA4-treated tumours. The high-affinity recombinant humanereered™ version, KB004, is now in Phase 1 clinical trials in hematological malignancies.

MECHANISMS UNDERLYING THE SYNERGISTIC APOPTOTIC ACTIVITY OF HDAC AND PROTEASOME INHIBITORS IN COLON CANCER CELLS.

This abstract has not been included at the request of the author

A SUBPOPULATION OF SLOW CYCLING, INVASIVE AND THERAPY RESISTANT MELANOMA CELLS IDENTIFIES EMT-LIKE PROCESSES IN MELANOMA

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Background: Melanoma is resistant to most standard chemotherapeutics through processes that are poorly understood. Hypothesized resistance mechanisms involve elevated drug efflux and metabolism, as well as decreased proliferation rates, as most chemotherapies target fast dividing cells.

Methods: Slow cycling and therapy resistant melanoma cells were isolated from multiple cell lines and subjected to additional functional assays. Both subpopulations were also analyzed by microarray and RNA-seq, and the resulting gene expression profile was interrogated for overlap and the presence of common motifs.

Results: The gene expression profiles of slow-cycling and chemotherapy resistant cells overlapped considerably, and were significantly enriched for gene sets expressed during invasion and EMT. The functions suggested by expression profiling are reflected in cellular behaviour, as the slow cycling, therapy resistant cells also comprise the invasive subset of cells. This subpopulation was capable of re-generating the original cell line heterogeneity, suggesting epigenetic establishment of the phenotypes. We identified a core network of ECM molecules in the slow-cycling cells which was preferentially expressed by cell lines featuring high levels of mesenchymal markers. Furthermore, epithelial-like melanoma cell lines could be induced to express the core gene network when EMT was induced by TGFbeta treatment.

Conclusions: Melanoma cell lines contain a subpopulation of slow cycling, invasive, therapy resistant cells, whose phenotype is related to EMT-like processes. We have identified a novel, melanoma specific gene network that might underpin this process, providing potential therapeutic targets on cells with a high potential to cause disease progression and relapse.
FLT3 LIGAND EXPANDS FOXP3+CD4+REGULATORY T CELLS IN HUMAN SUBJECTS
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CD4+CD25+FoxP3+ naturally occurring regulatory T cells (nTregs) play a crucial role in the maintenance of immune tolerance and in preventing autoimmune pathology. Interventions which expand nTregs are highly desirable, as they are thought to offer novel treatment options in a variety of autoimmune and transplantation settings. Paralleling previous pre-clinical studies, we demonstrate here that administration of the hematopoietic growth factor Flt3L to human subjects increases nTreg frequency, and reduces the ratio of CD8+ T cells to nTregs, in the peripheral blood. The increase in nTreg frequency was due to enhanced nTreg proliferation rather than release of nTregs from the thymus. Further studies revealed that Flt3L-induced proliferation of nTregs was an indirect effect which occurred via interaction of nTregs with the Flt3L-expanded pool of CD1c+ myeloid dendritic cells (DCs). Finally, the increased nTregs were found to be as suppressive in a proliferative assay as those collected from samples prior to administration of Flt3L. On the basis of these findings, Flt3L may be a promising agent for promoting immune tolerance in a variety of clinical settings.

CD133 EXPRESSION ON THE SURFACE OF MELANOMA CELLS IS PARALLELED BY CO-ORDINATED CHANGES IN GENE-EXPRESSION
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Malignant melanoma is responsible for the majority of skin cancer deaths. An increasing incidence and lack of successful therapeutic options for advanced disease highlight the need to further our understanding of melanoma. “Cancer stem cells” have been identified in a variety of solid tumours using the haematopoietic stem cell marker CD133. While the main functions of CD133 remain unknown, much interest has been focussed on CD133+ melanoma cells and their role within disease development and progression.

Methods: FACS-sorted CD133+ and CD133- populations from an early passage melanoma cell line were obtained for parallel culturing. We established cell blocks for immunohistochemistry analyses and isolated RNA at various culture time-points to gain insight into the kinetics of CD133 expression and co-regulated genes over time. Continuous analysis by immunohistochemistry, flow-cytometry and microarray analysis was performed over 12 weeks.

Results: While CD133+ cells were able to generate both CD133+ and CD133- cells; CD133- cells only gave rise to CD133- cells in vitro. Protein expression of CD133 decayed during culture; paralleled by co-ordinated changes in gene-expression.

By utilising microarray technology, multiple genes including RASSF2, SPATS1 and SLC16A3 have been identified to be co-regulated with CD133. IHC revealed that the cancer-testis antigen NY-ESO-1 expression directly correlates with CD133.

Conclusions: We have demonstrated that; while not necessarily being a stem cell marker; CD133 marks a cellular subpopulation with a distinct gene-expression pattern which is temporally co-regulated with the expression of CD133. This finding has the potential to shed light on the role of CD133 in melanoma.

IDENTIFYING EXTRACELLULAR THERAPEUTIC TARGETS ON MELANOMA CELLS

This abstract has not been included at the request of the author.
PAK1-KNOCKDOWN SUPPRESSES PROLIFERATION AND THE EPITHELIAL-MESENCHYMAL TRANSITION (EMT) IN VITRO & IN VIVO.

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Introduction: p-21-activated kinase 1 (PAK1) belongs to a group of six serine/threonine kinases that relay signals in many cellular pathways known to play vital roles in cell proliferation, motility and apoptosis. PAK1 is overexpressed in many cancers and the fact that its expression increases with colorectal cancer (CRC) progression highlights the importance of its role in tumour growth.

Aim: This project aimed to test the hypothesis that PAK1-knockdown would reduce CRC cell proliferation both in vitro and in vivo.

Materials and Methods: PAK1-knockdown cells were generated by transfecting shRNA insert sequences into human CRC cell lines DLD1 & HCT116.

PAK1-knockout mice were generously provided by Dr Chernoff from Fox Chase Cancer Center, Philadelphia, USA. Proliferation was assessed by cell counting and colon crypt height in CRC cells and mice respectively. Protein expression was detected by Western Blot.

Results: PAK1-knockdown decreased proliferation of CRC cells in vitro. PAK1-knockdown reduced the expression of the transcription factor ZEB1 and vimentin, overexpression of which has been shown to promote metastasis in CRC cells. Absence of PAK1 attenuated the total amount and nuclear accumulation of β-catenin and also c-Myc transcription. The colonic crypt height in PAK1-knockout mice was significantly reduced compared to wild-type mice.

Conclusions: We have demonstrated a role for PAK1 in tumour progression through modulating the expression of proteins that are major regulators of the EMT. Since invasion and metastasis of many tumours of epithelial origin including CRC requires the acquisition of many mesenchymal characteristics, our data has significant implications for PAK1 as a therapeutic target for regulating tumour metastasis.


(3) ZEB1 in Pancreatic Cancer. Wellner et al. Cancers 2010, 2, 1617-1628
BALANCE AND MOBILITY DYSFUNCTION, AND FALLS RISK IN OLDER PEOPLE WITH MILD-MODERATE ALZHEIMER'S DISEASE

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Aim: To identify differences in mobility and balance performance between people with mild to moderate severity Alzheimer's disease and age and gender matched older people.

Methods: Twenty-eight community dwelling participants (mean age 81, 37% males) with mild to moderate Alzheimer's disease (AD) and 28 cognitively intact age and gender matched controls were recruited. A comprehensive balance and mobility assessment involved computerised posturography measures of static and dynamic balance under various conditions; clinical measures included simple balance and mobility tests, and measures of falls and falls risk (Physiological Profile Assessment-PPA, the Falls Risk for Older People-FROP-Com).

Results: The AD group had a greater risk of falling measured by the PPA (p=0.006) and the FROP-Com (p<0.001). The AD group also had a significantly reduced balance performance, particularly when controlling balance with limited sensory information and in dynamic balance conditions where they demonstrated slower, shorter and less coordinated movement of the Centre of Gravity (p<0.05). They also had significantly poorer gait and mobility performance, presenting as slower speed in either general walking or walking involving turning tasks, with a marked deterioration found during dual tasks.

Conclusions: Balance dysfunction is common and affects various domains of balance performance in people with mild to moderate AD. Balance screening should be routine for patients with mild to moderate AD, at a stage of the dementia pathway when these patients are more likely to be able to safely undertake a balance training exercise program, which may have benefits that extend into later stages of the disease progression.

COMMUNITY MOBILITY RELATES TO WALKING SPEED POST STROKE

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Aims: To investigate if community mobility relates to walking speed in people with stroke. Method: Community mobility and walking speed of 15 community dwelling participants with stroke were contrasted to those of 15 healthy controls matched for age, sex and height. Walking speed was measured on level and sloped surfaces using the GAITRite system. Community mobility was self-reported using the Environmental Analysis of Mobility Questionnaire (EAMQ). The EAMQ rates the amount of “avoidance” and “encountering” of common mobility tasks from 1 (never) to 5 (always). The relationship between community mobility and walking speed post-stroke was then examined using spearman rho.

Results: People with stroke walked significantly slower on all surfaces than controls (p < 0.001, eg. mean difference on level surface = 67.6 cm/s, 95% CI 45.0 to 90.1). Community mobility was reported to be significantly less for participants with stroke than controls (p < 0.001). Median (range) EAMQ-Avoidance scores were: 2.2 (1.4 to 4.7) for stroke and 1.1 (1 to 2) for controls. EAMQ-Encounter scores were: 2.6 (1.5 to 4.1) for stroke and 4.1 (3.5 to 5) for controls. For people with stroke, walking speed related strongly to both EAMQ-Avoidance (r_s = -0.81) and EAMQ-Encounter (r_s = 0.81) scores. Conclusion: People with stroke walk more slowly on slopes and level surfaces than healthy matched controls. People who walk slowly tend to avoid more mobility tasks and venture less into the community. Walking speed requires attention during stroke rehabilitation to optimise community mobility.
MOBILITY AND FALLS AFTER DISCHARGE FROM STROKE REHABILITATION

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Aim: This study aimed to: 1) document longer term walking ability for people with stroke who could walk when discharged from inpatient rehabilitation; and 2) determine if walking and standing balance capacity at inpatient discharge predicted falls or avoidance of mobility tasks after discharge. Method: Thirty community-dwelling people with stroke who could walk unassisted when discharged were reviewed ≥ 6 months post-discharge. Balance and walking ability was measured using the 6-Minute Walk Test (6MWT), Four Square Step Test (FSST), Step Test (ST), Environmental Analysis of Mobility Questionnaire (EAMQ), Falls Efficacy Scale-International (FES-I) and self-reported falls. Results: Walking endurance significantly improved between discharge and follow-up (MD = 110.1m; 95% CI 70.8-149.4). Levels of avoidance for mobility tasks varied (EAMQ median = 2, IQR 1.3-2.9). Falls were reported by 12 (40%) participants. Cut-off scores that identified people at risk of falling were: a fail or taking more than 15s on the FSST; less than 10 steps on the ST; and walking less than 250m on the 6MWT. These cut-off scores showed good sensitivity and specificity for falls. People performing below the cut-off values at discharge avoided more mobility tasks and were more concerned about falling at follow-up. Conclusion: Walking endurance can improve after discharge from inpatient stroke rehabilitation. Despite this, people with stroke remain below average for walking endurance and many avoid mobility tasks in the home and community. Falls are common post-discharge, and may be predicted at inpatient discharge using cut-off values for clinical tests of standing balance and walking endurance.

EVIDENCE BASED PRACTICE (EBP) IN REHABILITATIVE PHYSIOTHERAPY

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There has been significant investment in resources, including development and access to online resources with the aim of developing a culture of evidence-based practice (EBP) in healthcare. Australian physiotherapists working within the public healthcare sector now have good access to a wide range of resources that support the application of an EBP approach to clinical practice. Despite EBP resources being readily available, it is still not well understood what level of knowledge and skills Australian physiotherapists have of EBP principles and concepts, and how well these principles and concepts are applied in clinical practice. This project examined physiotherapists' attitudes and beliefs, knowledge and skills in the principles of EBP via a survey. Survey results indicate that participants had an awareness of EBP, and related activities. The frequency and confidence with which EBP is undertaken varied widely and may be related to:
· undergraduate training and education
· specific skills such as literature searching and critical appraisal of literature
· formal EBP training and education
· years since graduation

The majority of participants surveyed believed that EBP has the potential to improve the quality of their practice, and are interested in improving knowledge and skills that underpin the application of EBP. Strategies that will build upon existing knowledge, skills and confidence in the area of EBP are required.

An EBP framework, which includes a set of procedures and targeted professional development to facilitate consistent and effective integration of EBP into physiotherapy clinical practice in rehabilitation, is therefore proposed.
DOES FEAR OF FALLING INCREASE AFTER FALLS IN PEOPLE WITH STROKE?

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Aim: Fear of falling is common in people with stroke. Most research has found associations between falls, fear of falling and function; however, the causality of this relationship has not been definitively established. The aims of this study were to determine the effects of falls and time on fall-related efficacy, gait, balance and activity in people with stroke at high risk of falls.

Methods: A longitudinal study was undertaken over 12 months with repeated measures of fall-related efficacy, gait, balance and activity at four-monthly intervals and following falls. Outcome measures included Falls Efficacy Scale – Swedish Modification (FES-S), gait speed, Step Test (ST), and Human Activity Profile (HAP). To examine the effects of falls and time, multi-level modelling was used.

Findings: Participants were part of an RCT evaluating falls prevention in people with stroke. Forty-eight people (mean age 70 years) were included in the analysis. Falls had no significant effect on FES-S when included in the model as a binary variable (parameter estimate 0.11, p=0.54) or as cumulative falls (parameter estimate 0.08, p=0.37). The change in FES-S per week was also non-significant (parameter estimate 0.0007, p=0.88). In contrast, significant decreases in gait speed, ST and HAP were seen after falls, ameliorated by improvement over time.

Conclusion: Contrary to expectations, fear of falling (as measured by fall-related efficacy) did not increase after falls. In addition, fear of falling did not change over time. Further research is needed to determine the characteristics of people with stroke who become more fearful after a fall.

THE NATURAL HISTORY OF WEIGHT CHANGE FOLLOWING A SPINAL CORD INJURY. A LONGITUDINAL, OBSERVATIONAL STUDY.

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Studies indicate 60% of Australians are overweight, 21% being obese1. This is reflected in the spinal cord injured (SCI) population who are at greater risk of weight gain than able-bodied persons.2 Initial weight loss due to hypermetabolism is often followed by a significant weight increase to exceed the premorbid state. Excess weight can lead to decreased independence, increased cardiovascular and diabetes risk and difficulties with equipment prescription.

This study tracked changes in body weight over two years following spinal cord injury and sought to identify the characteristics of those prone to weight gain or loss.

All patients admitted to the VSCS with a new SCI, aged 14 to 70 years, and able to give consent were eligible for inclusion. Participants were weighed and measured on admission and again at 4, 8 12 weeks, then 6, 12 and 24 months post injury.

69 patients were recruited.
33 quadriplegics, 36 paraplegics
47 with ASIA AB, 22 with ASIA CD
60 male, 9 female

A significant decrease in BMI was seen in the ASIA AB paraplegic group from admission 25.67 (+/- 5.07) to 12 weeks 23.56 (+/- 6.43).

There was a significant increase in abdominal circumference of the quadriplegic ASIA AB group from admission 89.32cm (+/-12.11) to 12 months 101.33cm (+/- 15.38) and in the paraplegic ASIA AB group from admission 87.80cm (+/- 13.07) to 12 months 95.23cm (+/- 14.65). There was also a significant increase in BMI for the combined paraplegic and quadriplegic ASIA AB groups from admission 25.1 (+/- 4.79) to 12 months 26.36 (+/- 4.86).

Our study has confirmed the initial weight loss expected during the acute phase following a SCI, and then weight gain at the 12 month mark. We also found an increase in abdominal circumference in the ASIA AB group, indicating increased risk of cardiovascular complications.

A REVIEW OF BENIGN PAROXYSMAL POSTITIONAL VERITGO (BPPV) IN PATIENTS ADMITTED TO THE ACQUIRED BRAIN INJURY (ABI) UNIT AT ROYAL TALBOT.

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Aims: Benign Paroxysmal Positional Vertigo (BPPV) is the most common cause of vertigo in adults. Head trauma has been described as a cause of BPPV, however, little has been recorded regarding the incidence in head injured populations. Aims of this retrospective review were to:

Determine the incidence and type of BPPV in patients admitted to the ABI unit over one year.
Document the response to treatment.

Method: Data was collected from physiotherapy assessment and treatment notes for all patients admitted to the ABI unit. Specific details regarding the type of BPPV, treatment techniques and response to treatment were collated.

Results: Data from 89 patients were collated. Forty-eight percent of all patients reported dizziness at some point during their inpatient stay with 30% of this group clinically diagnosed with BPPV. All cases of BPPV were related to patients with traumatic brain injury with 17.8% of this diagnostic group affected. Fifty-four percent of patients with BPPV had bilateral symptoms. Thirty percent of patients treated had resolution of symptoms after a single treatment while 70% required multiple treatment sessions.

Conclusion: The incidence of BPPV in this cohort of patients was higher than an incidence of 2.4% that has been suggested for the general adult population. The results highlight the potential prevalence for BPPV as a cause of dizziness in the traumatic brain injured population. The degree of bilateral BPPV and the high percentage of patients requiring multiple treatment interventions highlight the increased complexity of treating BPPV in this population.

DELAYED MOBILISATION IS ASSOCIATED WITH INCREASED RISK OF POST-OPERATIVE PULMONARY COMPLICATIONS FOLLOWING HIGH RISK UPPER ABDOMINAL SURGERY

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Background: Previous studies have shown that post-operative pulmonary complications (PPCs) occur in 13% of open upper abdominal surgical patients. We assessed the incidence and risk factors contributing to PPCs in a high risk open upper abdominal surgical cohort, and the barriers to early mobilisation. Methods: We conducted a prospective observational study of 72 patients who were a sub-set of a larger trial evaluating an enhanced model of medical co-management. We assessed the incidence of PPCs and physiotherapy intervention daily in the immediate post-operative period. Results: The incidence of PPCs was 38.9%. Incision type and time to mobilise away from the bed were independently associated with a diagnosis of PPC. For each post-operative day patients did not mobilise away from the bed, they were 3.03 (95% confidence interval 1.16-7.96) times more likely to develop a PPC. On the first post-operative day 52% of patients had a barrier to mobilisation. The most common barrier reported was hypotension. Development of a PPC was associated with a longer median hospital length of stay (16 versus 13 days; p = 0.046). Conclusion: The incidence of PPCs in this study was higher than several previous Australian and international reports and was associated with an increased length of hospital stay. This study is the first to demonstrate an increased risk of PPC with a delay in time to mobilise in the post-operative period. The role of early mobilisation in preventing the development of PPCs in a high risk upper abdominal surgical cohort requires further investigation.
ANKLE PLANTAR-FLEXOR POWER IN HUMAN GAIT.
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In human gait the majority of mechanical work is generated by the ankle joint. It is commonly thought that concentric contraction of the ankle plantar flexors is the mechanism behind A2 power generation. This study investigated the relationship between the EMG activity of the ankle plantar flexor muscles and A2 power generation. The gait patterns of six healthy adults were recorded. The following gait measures were extracted with respect to stance time: point of A2 power generation and A2 peak power, EMG activity of the gastrocnemius medialis (GM), gastrocnemius lateralis (GL), soleus (SOL) and peroneus longus (PL) muscles. On average, peak A2 power generation occurred 14% (as a percentage of stance time) post EMG peak activity of the plantar flexor muscles. At the point of A2 peak power generation, respective EMG activity of the SOL and PL muscles were 62% and 74% of the maximum activity recorded during stance. These results show that A2 ankle power is partly produced by concentric action of the ankle plantar flexor muscles. It also shows that passive return of elastic energy stored in these muscles (previous to the heel-off event) may play a major role in producing A2 power.

SPEED EFFECT ON JOINT POWERS IN AGEING GAIT.
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Ankle plantar flexor (A2), hip extensor (H1) and hip flexor (H3) joint power generation are important factors in human gait. It is well known that gait speed and ageing alters joint kinetics during walking. Ageing gait has been associated with decreased ankle joint function and increased hip muscle activity. However, it is not known whether this effect of speed upon joint kinetics is the same for older and young adults. This study investigated the effect of speed on A2, H1 and H3 joint powers in a group of young and older adults walking over a range of speeds. Participants walked at seven speed conditions. Peak joint powers were calculated and regressed as a function of gait speed. All joint powers were affected by speed. The older adults increased H3 more than the young adults, whereas the young adults increased A2 more than the older group. At speeds over 1.5 ms⁻¹ the older group increased cadence more than the younger group, whereas the younger group increased step length more than the older group. This shows that the older adults relied more on hip flexor muscles and increases in cadence to reach a maximum walking speed.

ASSESSING ACUTE AGED-CARE PATIENTS FOR THEIR RISK OF FALLS IN THE COMMUNITY PRIOR TO DISCHARGE
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Physiotherapy, Austin Health, Heidelberg, VIC, Australia

Introduction: Thirty percent of community dwelling adults over 65 years of age fall at least once per year, and the risk is greater after an acute illness. The aim of this study was threefold: to quantify falls risk of patients discharged from an acute aged care ward; to identify risk factors that correlate with falls risk for this population and to evaluate the suitability of the Falls Risk in the Community assessment tool (FROP-Com) to measure falls risk for these patients. Method: Fifty-two patients on Ward 10 were assessed using the FROP-Com prior to discharge into the community. Patients were classified as high, medium or low falls risk. Correlations between risk factors and overall falls risk were calculated using Pearson's r and time to complete the FROP-Com was recorded. Results: The FROP-Com took 10-30 minutes to complete. Thirty-five percent of patients were at high falls risk and 40% at moderate falls risk. Falls history and impaired balance (r > 0.600, p < 0.000) were moderately correlated with falls risk. Frequent over-night toileting, recent loss of appetite and poor cognition(r > 0.300, p<0.030) showed fair correlation with falls risk. Conclusion: People admitted to Ward 10 were at moderate to high risk of falls upon discharge. The FROP-Com is too time-consuming to complete on all patients, however results highlight risk factors that should be routinely considered in community dwelling older patients admitted to hospital. Patients with a falls history or impaired balance would benefit from more detailed falls risk assessment.
**OA HIP AND KNEE SERVICE**

**N. Peake, D. Di Natale**

*OA Hip and Knee Service, Austin Health, Heidelberg, Australia*

Introduction Austin Health has been running an Osteoarthritis Hip and Knee Service (OAHKS) since August 2008.

Problem Identification Waiting times for initial assessment by an orthopaedic specialist and for joint replacement surgery at Austin Health have been protracted. This may lead to further worsening of a patient's condition. Many patients with OA of the hip or knee were being referred for joint replacement at Austin Health without having trialled appropriate conservative management. Background The OAHKS is a new service delivery model developed in a DHS initiative to improve access, reduce waiting times, and improve active management of waiting lists for joint replacement surgery. It incorporates the Hip and Knee Questionnaire and resultant MAPT Score – a measure of the patient's OA disease severity and their priority for surgery. What did we change? Most newly referred patients to the Orthopaedic Department with either hip or knee osteoarthritis (OA), are assessed initially in the OAHKS by a Musculoskeletal Coordinator rather than waiting for an Orthopaedic specialist.

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**THE F-ASTEX: A NEW TOOL FOR MEASUREMENT OF TACTILE DISCRIMINATION OF THE FOOT.**

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Loss of foot sensation is an important factor contributing to disability in conditions such as diabetes. Screening and quantifying sensation impairment is important for diagnosis and treatment. Our multidisciplinary team has developed a prototype for assessment of foot sensation (the F-AsTex) based on the AsTex®, a clinical device with established reliability and sensitivity for hand sensation assessment. The F-AsTex prototype incorporates the capacity to quantify texture discrimination and pressure through the foot. Work is currently underway to refine assessment procedures and to evaluate the clinical utility of the F-AsTex for the assessment of foot sensation in people with diabetes.

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**SELF REPORTED PHYSICAL ACTIVITY LEVELS, FITNESS AND MUSCLE STRENGTH OF PEOPLE WITH NON-SMALL CELL LUNG CANCER: PRELIMINARY ANALYSES.**

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Questions: How physically active are people with lung cancer? How does this compare with recommended physical activity guidelines for Australians? Is there a change in physical activity, fitness or muscle strength over a 10 week period following diagnosis? Design: Prospective longitudinal cohort study. Participants: To date, 15 people (11 male), mean +/- SD age 68.1+/−10.5 years, lung capacity (FEV1) 79.1+/−19.7% predicted, body mass index (BMI) 25.8+/−6.4 kg/m² with stage I to III non-small cell lung cancer, recruited from three tertiary hospitals. Outcome measures: Time points: baseline (pre-treatment) and 10 weeks post diagnosis. Measures: Self reported physical activity measured using the Physical Activity Scale for the Elderly. Fitness measured using cardio-pulmonary exercise testing (VO2peak) and 6-minute walk test (6MWT). Upper and lower limb muscle strength. Results: Preliminary analyses of the first 15 participants demonstrated that at baseline 46.7%, 20.0% and 33.3% of participants were engaged in 'sufficient', 'insufficient' and 'sedentary' levels of physical activity respectively. Fewer participants were engaged at baseline in 'sufficient' levels of activity (compared with 54.1% Australian data) and more participants were classified as 'sedentary' (compared with 17.9% Australian data). In participants at baseline, mean +/- SD VO2peak was 16.1+/−4.3 ml/kg/min and 6MWT was 449.0+/−98.9m. At follow-up (n=10, 30% during chemotherapy, 70% post-treatment) only 6.7% of participants were engaged in 'sufficient' levels of physical activity. The 6MWT had declined by a mean +/- SD of 29.0+/−47.1m and muscle strength had declined in lower limb muscle groups. Conclusion: At diagnosis most participants did not meet the physical activity guidelines. Physical activity, fitness and muscle strength had declined at the 10 week follow-up.
TASTE CHANGES IN RENAL FAILURE
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Aim: To determine any associations between changes in salivary composition and altered taste perception in chronic renal failure.

Background: Saliva is composed of a number of taste active compounds which plays a vital role in taste stimulation. Chronic kidney disease (CKD) patients have an impaired ability to recognise basic tastes and salivary composition differs with CKD. The link between salivary composition and variation in taste sensitivity is unknown.

Methods: Thirty CKD patients (24 males, 6 females, age 69.7 ± 14.2yrs, glomerular filtration rate (GFR) <25mL/min) and five healthy controls (1 male, 4 females, age 44.6 ± 10.3yrs, GFR> 80mL/min) were recruited from the Austin Hospital outpatient renal clinic. A saliva sample was collected to determine biochemical composition. Participants performed a taste identification task to assess perception of the five basic tastes and completed a symptom questionnaire regarding taste changes.

Results: CKD patients had increased salivary bicarbonate, potassium and urea concentrations (p<0.05) and a poorer ability to perceive sour, glutamate and bitter tastes (p<0.05) compared to controls. Correlation analysis revealed bicarbonate concentration was inversely related to liking and intensity of glutamate taste and to the intensity of sour taste (p<0.05). Salivary urea was linked to the perceived intensity of bitter taste (p<0.05). Forty-three percent of patients indicated their symptoms contributed to decreased food intake.

Conclusions: This study provides evidence that taste active compounds present in the salivary fluid, in particular bicarbonate and urea are associated with taste perception and may influence taste function. Further research is required to clearly establish the link between reduced taste sensitivity and food intake in CKD patients.

CARDIAC TROPONIN T AS A PREDICTOR OF LONG TERM MORTALITY IN PATIENTS UNDERGOING HAEMODIALYSIS
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Aim: Compare the association of a single elevated cardiac troponin T (cTnT) to two consecutively elevated cTnT with long term mortality in haemodialysis patients.

Background: Abnormal cardiac troponin concentrations are associated with increased mortality in asymptomatic haemodialysis patients. However, cTnT levels may vary and two elevated levels may better predict mortality than a single measurement.

Methods: The vital status of 100 haemodialysis patients who had two cTnT measurements three months apart was ascertained. cTnT≥0.04 µg/L measured by the Roche TnT assay was considered abnormal. Survival was compared by the Log-rank test and hazard ratios calculated after log-term follow-up, and at earlier time periods. Patients with a single cTnT≥0.04 µg/L were compared to those with cTnT<0.04 µg/L, and patients with two consecutive cTnT≥0.04 µg/L were compared to patients who had <2 such levels.

Results: 45/100 patients died over a median follow-up of 5 years, and 47 had cTnT≥0.04 µg/L. 25/47 (53.19%) with cTnT≥0.04 µg/L died versus 20/53 (37.74%) without cTnT≥0.04 µg/L (HR 1.29, 95%CI 0.71-2.32, P=0.399). 44/96 with two consecutive samples died and 40 had two consecutive cTnT≥0.04 µg/L. 24/40 (60%) with two consecutive cTnT≥0.04 µg/L died versus 20/56 (35.71%) with <2 consecutive cTnT≥0.04 µg/L (HR 1.71, 95%CI 0.94-3.09, P=0.077). Two consecutive cTnT≥0.04 µg/L were significantly associated with greater mortality at earlier time points (2 and 3 years [HR 3.49, 95%CI 1.23-9.91, P=0.019; and HR 3.44, 95%CI 1.32-8.94, P=0.011 respectively]).

Conclusion: Single or two consecutive cTnT≥0.04 µg/L are not associated with greater mortality in dialysis patients over long-term follow up. Consecutive cTnT≥0.04 µg/L is strongly associated with mortality when restricted to 3 year follow-up.
FAILURE OF PROTEOLYSIS AS A NOVEL MECHANISM FOR TUBULAR PROTEINURIA IN MICE AND HUMANS LACKING THE INTRINSIC LYOSOMAL PROTEIN SCARB2/LIMP-2

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Deficiency of the intrinsic lysosomal protein SCARB2 causes collapsing FSGS and renal failure in humans. Limp-2-/- (the murine homologue of SCARB2)mice develop tubular proteinuria but not FSGS. Previous studies have shown unchanged expression and function of the megalin/cubilin tubular protein uptake system in the proximal convoluted tubules (PCT). To determine whether humans with SCARB2 mutations also have tubular proteinuria, urine from two human subjects with SCARB2 mutations but no renal failure was obtained. To mechanism the mechanism for tubular proteinuria, immunofluorescence labelling was performed on kidney sections from WT and Limp-2-/- mice and examined by confocal microscopy. The software NIH ImageJ 1.34 was used to quantify the distribution of labelled proteins in the PCT and the degree of co-localisation by calculating Manders’ coefficient. Urine from one of the patients had tubular proteinuria. Limp-2-/- mice had increased basolateral distribution of LAMP-1, a late endosome/lysosome marker, and retinol-binding protein (RBP), a low molecular weight protein reabsorbed by the PCT, indicating failure of protein degradation after uptake (P<0.0001 for both). Injected bovine serum albumin (Alexa-BSA) was also persistent in the PCT of Limp-2-/- mice. Both exogenous Alexa-BSA and endogenous RBP showed reduced co-localisation with the lysosomal protease cathepsin B in Limp-2-/- mouse kidneys (Manders' coefficients P<0.0001). The data suggest that tubular proteinuria in Limp-2-/- mice and humans with SCARB2/Limp-2 mutations is due to failure of endosomes containing reabsorbed proteins to fuse with lysosomes in the PCT. Failure to digest reabsorbed proteins in the PCT is a previously undescribed mechanism for tubular proteinuria.

ASSOCIATION OF JOINT HYPERMOBILITY AND ORTHOSTATIC INTOLERANCE WITH POLYCYSTIC KIDNEY DISEASE IN TWO UNRELATED INDIVIDUALS

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Background: Joint hypermobility is associated with chronic fatigue syndrome, gastrointestinal dysmotility and disorders of postural blood pressure (BP) control i.e. postural orthostatic tachycardia syndrome (POTS). Postural intolerance can be exacerbated by anti-hypertensive agents and can therefore contribute to medication non-adherence. BP control is of special importance in patients with chronic renal disease. We report two unrelated patients with polycystic kidney disease (PKD) who had uncontrolled hypertension because of medication non-adherence secondary to postural intolerance.

Methods: PKD was diagnosed by renal ultrasound. Clinic BP was measured non-invasively over 5 minutes of standing preceded by 5 minutes supine rest. Ambulatory BP and pulse rate were measured with the Spacelab device. Joint hypermobility was defined by the Beighton Score (normal <4/9).

Results: Our patients (a 27 year-old male and a 50 year-old female) have PKD confirmed on renal ultrasound and both had a positive family history. Both patients had stopped or limited anti-hypertensive therapy because of postural symptoms. Both were hypermobile with a Beighton Score of 4/9. On ambulatory BP monitoring, their average treated daytime BP was 158/112 mmHg and 141/100 mm Hg respectively. Neither had documented postural hypotension however the male patient had a postural pulse rate rise of 35 bpm – thus satisfying the criteria for POTS.

Conclusion: An association between joint hypermobility, postural intolerance and PKD has not been reported previously. In both our patients, postural symptoms were sufficient to interfere with anti-hypertensive treatment. Further studies should be directed to confirming if this association is representative of other patients with PKD.
REDUCED ASSOCIATION OF THE METABOLIC REGULATORS AMPK AND ACC1 WITH NKCC2 IN MICE FED A HIGH FAT DIET

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Aim: To determine the effect of a high fat diet on AMP-activated protein kinase (AMPK) in the kidney.

Background: Rodents fed a high fat diet develop obesity, hypertension and hyperreninaemia, so acting as a good model for human obesity-related hypertension. AMPK has a central role in regulation of fatty acid metabolism through phosphorylation of acetyl CoA carboxylase 1 (ACC1) on Ser79. AMPK and ACC1 also bind to the salt co-transporter NKCC2 (the target for frusemide), and AMPK influences the co-transporter activity of NKCC2. NKCC2 also detects tubular salt concentrations to influence renin secretion. In this study, therefore, we determined the effect of a high fat diet on AMPK and NKCC2 in the kidney.

Methods: Male and female C57Bl/6 mice were fed normal chow or a 23% fat diet for 16 weeks (n=12 per group). Mice were then sacrificed and kidneys harvested for assay of AMPK activity, ACC1 and NKCC2 phosphorylation, as well as co-immunoprecipitation of AMPK and ACC1 with NKCC2.

Results: Both male and female mice gained significantly more weight than controls fed normal chow (p<0.05). There was also a significant increase in plasma renin concentration in both groups compared with controls (p<0.0001). There was no change in AMPK activity or ACC1 phosphorylation in whole kidneys. Immunoprecipitation of NKCC2, however, revealed that there was reduced association of AMPK, ACC1 and pACC1 with NKCC2 in mice receiving a high fat diet.

Conclusion: This data suggests that changes in the association of NKCC2 with AMPK and ACC1 could contribute to the increase in renin secretion seen in mice receiving a high fat diet.
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COMPARISON OF RENAL PRECONDITIONING TECHNIQUES IN A RAT MODEL
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Introduction: Between 5-17% of renal surgery patients suffer from deterioration in kidney function following surgery due to temporary disruption in oxygen and blood supply (ischemia). Using a rat model of ischemia our goal is to determine whether preconditioning of kidney tissue by either stimulating hypoxia inducible factor (HIF1α) or transient hypoxia (intermittent clamping) prior to ischemia, can reduce subsequent kidney injury. HIF1α is a master regulator of 200 functionally diverse genes involved in cell survival, apoptosis, erythropoiesis, angiogenesis and energy metabolism.

Methods: HIF1α was stimulated by 30 mg/kg subcutaneous injection of cobalt chloride 24 and 6 hours prior to ischemia. Intermittent clamping consisted of 5 minutes renal artery clamping followed by 10 minutes reperfusion over 4 cycles. Following preconditioning all rats underwent 40 minutes of renal artery clamping. Serum renal function tests and animal health assessment scores were used as a measure of renal impairment. Results: Ischemia resulted in serum urea and creatinine rise which peaked between day 1 and 3 with a return towards basal levels at day 7. Cobalt treated rats had the lowest rise in serum urea and creatinine compared with the control group (p<0.05). Rats which received intermittent clamping alone or in combination with cobalt treatment had also a lower rise in serum urea and creatinine as compared to control. Whilst the control group had a 50% mortality rate, no rats in the preconditioning groups died (p<0.05). Conclusion: Development of hypoxia-mimetic agents which upregulate HIF1α pathway would offer the greatest benefit in renal preconditioning for clinical application.

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FOXP3+ T CELLS IN PERIPHERAL BLOOD OF RENAL TRANSPLANT RECIPIENTS AND CLINICAL CORRELATIONS
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2Surgery, Austin Health, Heidelberg, VIC, Australia
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Aim. Immunophenotype peripheral blood T cells from renal transplant recipients (RTR) using cellular markers of regulatory T cells (Tregs) and flow cytometry, including Foxp3, and correlate these findings with clinical parameters.

Methods. Expression of phenotypic markers of Tregs was assessed by flow cytometric analysis of peripheral blood lymphocytes (PBLs) from (a) RTR (n=95), (b) patients with end-stage renal failure (ESRF) awaiting transplantation (n=17) and (c) normal healthy controls (NHC) (n=6).

Results. The proportion of CD4+CD25+Foxp3+ cells within the CD4+ cell population did not significantly alter at different time points post-transplant. However, the percentage of both CD4+CD25+Foxp3+ and CD4+CD25+ cells within the CD4+ population were significantly lower in RTR compared to patients with ESRF and NHC. In contrast, RTR and patients with ESRF had a higher proportion of CD4+CD25+ cells expressing Foxp3, compared to NHC. Multivariate analysis of PBL phenotypes and clinical parameters demonstrated (a) a positive linear relationship between the proportion of CD4+CD25+ cells expressing Foxp3 and estimated glomerular filtration rate (eGFR) (b) a higher percentage of CD4+CD25+ cells in patients with malignancy, which correlated strongly with time post-transplant and age of the RTR.

Conclusion. Immune monitoring of the PBL phenotype in RTR using CD4, CD25 and Foxp3 may stratify RTR and predict graft outcome and function, and risk of complications from immunosuppression. Longitudinal and functional studies of Tregs are essential to extend the findings of the present study.
THE VALIDITY OF SELF-REPORTED DYSPHAGIA IN PATIENTS ATTENDING PULMONARY REHABILITATION PROGRAMS

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Background: Impaired coordination between respiration and swallowing places patients with COPD at an increased risk of aspiration. The current practice in Australia, is that patients undergoing pulmonary rehabilitation are screened for dysphagia via self-report questionnaires. No valid standardised dysphagia-screen currently exists for use in this population.

Aim: To investigate the validity of the current dysphagia screen used in pulmonary rehabilitation at Austin Health by determining the predictive value of both specific questions and overall pass/fail result with findings of dysphagia on clinical and instrumental assessments.

Method: Medical histories of Pulmonary Rehabilitation participants (November 2002 – February 2011) were retrospectively audited for questionnaire responses and clinical and instrumental assessment of presence/absence of dysphagia.

Results: Four hundred and ninety six patients completed self report dysphagia screening; 96 completed clinical swallowing assessments; and 34 instrumental swallow assessments. The positive predictive value (PPV) of a fail result on screening and diagnosis of dysphagia on clinical assessment was 69% (95%CI 58-78%) and on instrumental assessment 76% (95%CI 59-89%). Significant odds ratios existed between dysphagia on clinical assessment and reports of food avoidance (p = 0.0027), food/fluids sticking (p = 0.0043) and dry mouth (p = 0.02). After adjustment for all other questions, age and predicted FEV1, only food avoidance remained significant (p=0.022) with a PPV of 86% (95%CI 70.5-95.33%) but a low negative predictive value (NPV) of 44.4% (95%CI 29.99-58.75%). The PPV of the 3 questions combined was 92.86% (95%CI 82.96%-100%).

Conclusion: Self reports of food avoidance, sticking and dry mouth show trends for use in future screening of dysphagia in pulmonary rehabilitation participants.

THE DIRECT AND INDIRECT EFFECTS OF DEPRESSION ON GLYCAEMIC CONTROL IN TYPE 2 DIABETES

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4Department of Endocrinology and Diabetes, St Vincent's Hospital, Fitzroy, VIC, Australia

Aim: Depression is common in patients with diabetes, and is associated with poorer glycaemic control. The purpose of this study was to investigate the direct and indirect effects of depression on glycaemic control in type 2 diabetes, and the relative influences of various psychosocial and biological factors. Method: In this cross-sectional study, 126 participants were recruited from Austin Health, Melbourne. Self-reported measurements of depression, self-efficacy, self-care activities (i.e., medication compliance, physical activity and diet) and diabetes management orientation (i.e., independence, dependence on others and excuse making) were collected. Path analysis, a statistical method for modeling hypothesized cause/effect relationships among a set of variables, was performed. Results: Path analysis revealed that depression decreased self-efficacy (p < 0.001), increased dependency (p < 0.001), and increased excuse-making (p = 0.010). In turn, dependency (p = 0.034) and excuse-making (p < 0.001) decreased compliance with a healthy diet, which was related to a higher HbA1c (p = 0.011). Additional factors that were related to elevated HbA1c levels included male gender, via poorer compliance with a healthy diet (p = 0.002), insulin use (p < 0.001) and the severity of diabetic complications (p = 0.034). Depression did not exert a direct influence on HbA1c levels. Conclusion: This study has developed a preliminary conceptual framework for understanding the interplay between psychosocial and biological predictors of mood, diabetes management and glycaemic control. While depression did not directly influence glycaemic control, depression indirectly influenced glycaemic control through suboptimal self-management orientation, which in turn resulted in detrimental self-care behaviours.
CARDIOVASCULAR RISK FACTORS AND REDUCED BONE DENSITY ARE HIGHLY PREVALENT AMONGST MEN COMMENCING ANDROGEN DEPRIVATION THERAPY.

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Androgen deprivation therapy (ADT), an effective treatment for prostate cancer, has been associated with accelerated bone loss, visceral fat gain and insulin resistance.

Aims: To evaluate bone and metabolic health in men with non-metastatic prostate cancer receiving ADT.

Methods: A retrospective review was performed of all men receiving long-term ADT who attended the Austin Health Men's Health Clinic (MHC) between 2007-2010. Baseline evaluation was performed within the first 6 months of ADT commencement, and men were followed for 2 years.

Results: 167 patients (mean age 69.9 years) were available for baseline evaluation:

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight or obese (Body Mass Index (BMI) ≥ 25kg/m²)</td>
<td>88.3%</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>40.0%</td>
</tr>
<tr>
<td>Current smokers</td>
<td>16.3%</td>
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<tr>
<td>Pre-existing hypertension</td>
<td>53.0%</td>
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<tr>
<td>Pre-existing diabetes</td>
<td>20.4%</td>
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<tr>
<td>Pre-existing hypercholesterolemia</td>
<td>47.3%</td>
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<tr>
<td>Pre-existing cardiovascular disease</td>
<td>30.5%</td>
</tr>
<tr>
<td>Vitamin D insufficient &lt;75nmol/L</td>
<td>73.4%</td>
</tr>
<tr>
<td>Osteoporosis (T score ≤-2.5)</td>
<td>11.8%</td>
</tr>
<tr>
<td>Osteopenia (T score -1 to -2.4)</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

Follow-up data after 2 years of ADT was available for 76 men. Weight increased by +2.0kg, BMI increased by +0.7 kg/m² (p=0.031), and waist circumference +4.23cm (p=0.003). Despite this, there was no significant change in fasting glucose, HOMA-IR or HbA1c. Systolic BP fell by -4.9mmHg (p=0.041), total cholesterol by -0.37mmol/L (p=0.005) and triglycerides by -0.23mmol/L (p=0.005), due to intervention with lipid-lowering and anti-hypertensive agents. Similarly, there was no change in bone mineral density (BMD). When stratified according to treatment, those not receiving anti-resorptive therapy (39 patients) had a significant fall in lumbar spine BMD (-0.061g/cm², p=0.033) and fall in total hip BMD (-0.019g/cm², p=0.011).

Conclusion: Given significant baseline risk, bone density and cardiovascular risk factors should be monitored routinely in men receiving ADT for non-metastatic prostate cancer. Adverse effects of ADT on metabolic and bone health may be reduced by proactive management.
LOW TESTOSTERONE AS AN INDEPENDENT PREDICTOR OF SURVIVAL IN MEN WITH CHRONIC LIVER DISEASE

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Objective: To examine prevalence and prognostic implications of low serum testosterone in men with chronic liver disease.

Methods: Retrospective database audit of 437 men presenting to the Austin Health Liver Clinic for evaluation for liver transplant between 2002 and 2010. Patients’ outcome of liver transplant or death were ascertained from hospital records. The study was approved by the Austin Health Human Research Ethics Committee.

Results: 171 of the 437 (39%) men had documented testosterone levels measured in the records. Selected baseline characteristics of the 171 men are shown in the Table. Overall, 61% of men had a low total testosterone (TT, <10 nmol/L, lower limit based on healthy young men), and 90% of men had a low calculated free testosterone (cFT, <230 pmol/L). During the available observation time (median 8 months, interquartile range 4-14 months), 56 men (33%) died, and 63 men (37%) received a liver transplant. Median time to death was 8 months (2-13), and to liver transplant 8 months (5-14). Baseline low TT (p=0.002) and cFT (p=0.005) predicted mortality. Cox proportional hazard model shows both low total (p< 0.02) and free testosterone (p< 0.0009) is predictive of death independently of other factors including the severity of liver disease (assessed by Model for End Stage Liver Disease (MELD) score), older age, and current ethanol use. The risk of death increased by 9% for every 1 nmol/L decrease of TT, and by 10% for every 10 pmol/L decrease of cFT.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alive</th>
<th>Died</th>
<th>Liver Transplant</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Pre-Tx (years)</td>
<td></td>
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</tr>
<tr>
<td>n=52</td>
<td>n=56</td>
<td>n=63</td>
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<td>55</td>
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<td>49 – 59</td>
<td>51 – 60</td>
<td>46 – 57</td>
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<td>BMI (kg/m²)</td>
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<td>25.9</td>
<td>26.8</td>
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<td>11 - 19</td>
<td>13 – 24</td>
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<td>TT (nmol/L)</td>
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<td>2.9 – 8.3</td>
<td>3.4 – 10</td>
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Values are median, interquartile range (Kruskal-Wallis rank sum test).

Conclusions: Low testosterone levels are common in men with severe liver disease. It predicts mortality independent of the MELD score which is currently being used for prioritizing allocation of liver transplants.
THE ROLE OF ANDROGENS IN THE PROGRESSION OF PROSTATE CANCER

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INTRODUCTION AND OBJECTIVES: Androgen deprivation therapy is a common treatment of prostate cancer. Previous studies have shown that dihydrotestosterone (DHT) the more active metabolite of testosterone, interacts with other proteins in a complex way to affect cell structure and function, but the mechanism of DHT in the promotion of prostate cancer metastasis is not clearly understood. We investigated the effects of DHT on the proliferation and motility of the androgen responsive human prostate cancer cell line LNCaP.

METHODS: Using a cell proliferation assay, LNCaP growth was tested by stimulating with 1nM and 10 nM of DHT at 24 hrs in charcoal stripped FBS (CS-FBS). LNCaP cells were also seeded into a 24 well plate BD Biocoat MatrigelTM Invasion Chamber (BD Bioscience) for 24 hrs prior to stimulation with 10 nM DHT. After 24 hrs and 48 hrs of incubation period motile cells were fixed and prepared into glass slides. In addition, stimulation of non androgen responsive cell lines PC3 and a less responsive androgen cell lines DU145 was conducted.I

RESULTS: It was found that cell proliferation and motility of LNCaP cells was significantly increased after stimulation by 10 nM of DHT at 24 hrs (p<0.01) and 48hrs (p<0.01), whilst DHT had minimal effect on control PC3 and DU145 cells.

CONCLUSIONS: We conclude that DHT influences the androgen responsive cell line LNCaP in increasing cell growth and motility and may play a role in metastasis. Currently, further experiments are being performed to examine the expression of CD151, a cell surface protein involved in prostate cancer cell migration (Ang et al 2010 ) to confirm the notion that androgens might stimulate prostate cancer cell motility via modulation of other promoters of cell invasion.

(1) Ang J et al. CD151 Protein Expression Predicts the Clinical Outcome of Low-Grade Primary Prostate Cancer Better than Histologic Grading, Cancer Epidemiology Biomarkers Prev. 2004. 13(11):1717-1721


LONG-TERM PERSISTENCE OF HORMONAL ADAPTATIONS TO WEIGHT LOSS

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Background: Following weight loss, changes occur in circulating levels of several peripheral hormones involved in the homeostatic regulation of body weight.

Aim: To examine whether these changes are transient or persistent following prolonged weight loss maintenance

Methods: Fifty non-diabetic overweight or obese subjects started a 10-week weight loss program using a very-low-energy diet (VLED), followed by 1 year of weight loss maintenance. Circulating concentrations of leptin, ghrelin, PYY, GIP, GLP-1, amylin, pancreatic polypeptide (PP), cholecystokinin (CCK) and insulin, and subjective ratings of appetite were examined at baseline, after initial weight loss, and at 1 year follow-up.

Results: Mean initial weight loss of 13.5 ± 0.5 kg led to reductions in leptin, PYY, amylin, CCK and insulin, and increases in ghrelin, GIP, PP and subjective appetite, which persisted at 1 year.

Conclusions: The compensatory changes in circulating mediators of appetite which encourage weight regain after diet-induced weight loss do not reverse 12 months after initial weight reduction.
THE EFFECT OF LACTATION ON BONE MICRO-ARCHITECTURE
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2Endocrine Centre of Excellence, Austin Health, Heidelberg, VIC, Australia
3Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, VIC, Australia

The structural basis of bone strength is determined during growth and the variation in bone strength is determined by both genetic and environmental factors. One of the most important factors contributing to the attainment of peak bone strength and its loss is sex hormones. Oestrogen deficiency increases bone remodelling and contributes to bone loss. While oestrogen deficiency appears at around midlife in women, lactation is accompanied by oestrogen deficiency and may be associated with bone loss. During lactation, bone resorption increases providing the neonate with calcium for skeletogenesis. I hypothesised that lactation results in a reduction of bone mineral density (BMD) and trabecular number and thickness but any decrease would be reversed following the cessation of lactation in women younger than 35 years, but not in those older than 35 years because remodelling may have become unbalanced (with less bone deposited than was removed during the remodelling cycle). I assessed the results of BMD and bone micro-architecture in the distal forearm and distal radius using high resolution 3D peripheral quantitative computed tomography in a study performed previously by my collaborators in 100 women aged 20–42 years. Three scans were taken: one at 14.7 days (range 2–25) post-parturition, one at 5.2 months (range 3–6) post-parturition during breastfeeding and one at 8.3 months (range 6–14) after the cessation of breastfeeding. Preliminary results show total BMD decreased by 0.04 SD. Cortical area, thickness and trabecular number decreased by 0.13, 0.1 and 0.3 SD respectively. Trabecular thickness and marrow area increased by 0.2 and 0.01 SD. Follow up is underway to determine whether these small structural deficits are reversed when lactation is stopped.

SIMULTANEOUS DETERMINATION OF FREE CATECHOLAMINE AND METANEPRINE LEVELS IN PLASMA OR URINE BY LIQUID CHROMATOGRAPHY WITH MASS SPECTROMETRIC DETECTION.
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2Clinical Pharmacology and Therapeutics, Austin Hospital, Heidelberg, VIC, Australia

Pheochromocytoma is a rare catecholamine producing tumour occurring in neuroendocrine tissue. Adrenaline and noradrenaline are the main catecholamines secreted by the tumours although some do secrete large amounts of dopamine. Diagnosis of pheochromocytoma is normally based on testing for elevated levels of one or more of these catecholamines in plasma or urine. However the levels of secreted catecholamines can vary dramatically with time and this coupled with their short half life in plasma results in variable concentrations. By contrast their main metabolites, metanephrine, normetanephrine and 3-methoxytyramine have longer half lives, are continually formed and are less susceptible to sampling or storage variation making their levels more reliable indicators of the presence of pheochromocytomas.

The Clinical Pharmacology Laboratory at the Austin Hospital has traditionally determined the levels of free catecholamines using liquid chromatographic separation coupled with electrochemical or fluorescence detection for plasma and urine respectively. The acquisition of a tandem mass spectrometer coupled to a liquid chromatography system has enabled the sensitive measurement of both catecholamines and their main metabolites simultaneously. Validation data will be presented.
RACIAL DIFFERENCE IN BONE MICROSTRUCTURE AND DENSITY AT DISTAL RADIUS AND TIBIA BETWEEN YOUNG CHINESE AND CAUCASIAN MEN

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Hip and forearm fracture rates are lower in Asians than Caucasians. We reported Chinese women have thicker cortices and trabeculae within a smaller bone than their Caucasian counterparts (Wang et al 2009). To define racial differences in bone microstructure in men, we studied 50 young healthy Chinese and 62 Caucasian men aged 18 to 50 years (mean age 36.3 vs 38.3 years) using high-resolution peripheral quantitative computed tomography (pQCT, XTreme CT, Scanco Medical AG, Bassersdorf, Switzerland).

Chinese men were shorter and weighed less than Caucasians. Radius total bone cross-sectional area (CSA) was less by 12.1% and (p<0.001) in Chinese than Caucasian men (5.7% after height and weight adjustment, p=0.075). Cortical and trabecular thickness and volumetric bone mineral density (vBMD) was similar by race. Trabecular number at the radius was less by 6.0% (p<0.05) in Chinese men but similar after height and weight adjustment. Similarly, trabecular number and bone volume/tissue volume (BV/TV) were also less by 7.3-7.8% in Chinese men at the distal tibia before but not after height and weight adjustment. The other bone microarchitecture at the tibia was similarly presented by race. Tibial CSA was 6.4% (p<0.05) smaller in Chinese men but not differed after height and weight adjustment. In conclusion, unlike women, Chinese and Caucasian men have very similar bone microarchitecture and density. We infer that the lower fracture risk in Chinese men may be explained by factors other than their bone structure in the young adulthood.


INVESTIGATING NON-DNA BINDING DEPENDENT SIGNALLING PATHWAYS OF THE ANDROGEN RECEPTOR

Medicine (Austin Health), University of Melbourne, Heidelberg, VIC, Australia

Androgens (testosterone and dihydrotestosterone (DHT)) bind to the androgen receptor (AR) and have many actions including increasing bone mineral density and reducing adiposity. AR binds DNA and directly regulates gene expression (genomic action). Non-DNA binding-dependent AR actions including indirect gene repression1 and activation of 2nd messenger cascades2 have been identified in vitro, although their physiological role is unknown. We aim to investigate non-DNA binding-dependent actions using our DBD-ARKO mouse model3, which has deletion of genomic DNA-binding-dependent AR actions.

The mutant AR binds ligand normally and retains the ability to phosphorylate ERK, with phosphorylation increased following 1 min 100 nM DHT treatment in wildtype and DBD-ARKO fibroblasts, and abolished by the AR antagonist bicalutamide. In contrast, the mutant AR cannot indirectly repress Mmp13 expression in fibroblasts, which may be due to its reduced nuclear translocation (33% vs wildtype 88%).

We examined effects of 10 weeks orchidectomy ± DHT treatment in wildtype and DBD-ARKO male mice. Consistent with the in vitro data, Mmp13 is repressed 40% by DHT in bone from wildtype but not DBD-ARKO males. DHT reduces ERK phosphorylation by 40% in DBD-ARKO bone. In subcutaneous fat, DHT reduces both CREB phosphorylation and levels in wildtype, but not in DBD-ARKO mice. However, Creb1 gene expression is repressed 33% by DHT in DBD-ARKO fat. As genomic AR actions are deleted in DBD-ARKO mice, DHT must act via non-DNA binding-dependent signalling to reduce Creb1 expression and ERK phosphorylation. This is the first evidence supporting the existence of non-DNA binding-dependent AR actions in vivo.

(1) Schneikert J et al. J. Biol. Chem. 271:23907-23913
(2) Unni E et al. Cancer Research 64: 7156-7168, 2004
(3) Notini AJ et al. J. Mol. Endo. 35:547-555, 2005
DEVELOPMENT OF A QUESTIONNAIRE ASSESSING SELF-MONITORING OF BLOOD GLUCOSE BEHAVIOURS AND INSULIN SELF-ADJUSTMENT BEHAVIOURS IN PATIENTS WITH DIABETES MELLITUS

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1Medicine, University of Melbourne, Melbourne, VIC, Australia
2Cardiology, Austin Health, Heidelberg, VIC, Australia
3Endocrinology, Austin Health, Heidelberg, VIC, Australia

BACKGROUND Currently there are no existing validated questionnaires that assess how patients with diabetes mellitus self-monitor their blood glucose and self-adjust their doses of insulin. Hence, the relationships between effective self-monitoring of blood glucose (SMBG), insulin self-adjustment and glycaemic control is unclear. The aim of this study was to develop a detailed self-report questionnaire to identify specific SMBG and insulin self-adjustment behaviours that are associated with poor glycaemic control.

METHOD A literature review was conducted to determine the content domains of effective SMBG and insulin self-adjustment. Questionnaire items were developed to represent each of these content domains, which were reviewed by an expert panel (diabetologist, cardiologist and psychologist) and a focus group to determine content and face validity. Forty-one items were selected and administered to study participants with type 1 or type 2 diabetes (n=123). Data was subjected to exploratory factor analysis and items with strong factor loadings (>0.5) were selected for inclusion in the final questionnaire. Subscores for each content domain were calculated and correlated with participants’ most recent HbA1c.

RESULTS Six factors were extracted in the factor analysis, with two higher order factors of SMBG routines and insulin self-adjustment. The six factors were monitoring routines, attitudes, pattern recognition, insulin adjustment based on daily activities, doctor adherence for insulin adjustment, and insulin adjustment based on pattern recognition. Subscores representing effective ‘insulin adjustment based on daily activities’ and high ‘doctor adherence for insulin adjustment’ were found to be associated with better glycaemic control after adjusting for confounding factors (β=−0.293 and -0.328), demonstrating external criterion related validity.

CONCLUSION Poor insulin adjustment based on daily activities and poor adherence to doctor advice for insulin adjustment were associated with worse glycaemic control. The SMBG routines and insulin adjustment questionnaire may be a useful tool to identify these behaviours associated with poor glycaemic control.

AN INVESTIGATION INTO THE ROLE OF HEALTH BEHAVIOURS AND ATTITUDES IN MEDIATING THE RELATIONSHIP BETWEEN DEPRESSIVE SYMPTOMS AND GLYCAEMIC CONTROL IN PATIENTS WITH DIABETES ON INSULIN

M. L. Kim1, A. Stewart1, G. Jerums3, R. MacIsaac3, D. L. Hare1,2

1Medicine, University of Melbourne, Melbourne, VIC, Australia
2Cardiology, Austin Health, Heidelberg, VIC, Australia
3Endocrinology, Austin Health, Heidelberg, VIC, Australia

BACKGROUND Previous studies have indicated that depressive symptoms are associated with poor glycaemic control in patients with diabetes, and the relationship may be mediated by health behaviours such as diet, physical activity and effective self-monitoring of blood glucose (SMBG). The objective of this study was to closely examine this relationship with detailed continuous scales to clarify the roles of these behaviours in mediating the relationship between depressive symptoms and glycaemic control, particularly in patients on insulin treatment.

METHODS A cross-sectional study was conducted using data collected from patients with type 1 or type 2 diabetes currently on insulin (n=78). Patients were administered 6 questionnaires relating to diet, physical activity and SMBG. Recent HbA1c data was collected by medical file review. Univariate and multivariate analyses were conducted to identify relationships between depressive symptoms, behavioural mediators and glycaemic control. Path analysis was conducted to examine and model the behavioural pathways mediating depressive symptoms and glycaemic control.

RESULTS Depressive symptoms were found to be significantly associated with glycaemic control (HbA1c) in patients with diabetes on insulin (r=0.239). Path analysis found that depressive symptoms and HbA1c level were not mediated by diet and physical activity in this sample. However, self-adjustment of insulin based on daily activities was found to be a statistically significant behavioural mediator of depressive symptoms and HbA1c.

CONCLUSIONS Diet and physical activity behaviours do not mediate the relationship between depressive symptoms and glycaemic control in patients with diabetes currently taking insulin. Greater dependence on others for diabetes management and self-adjustment of insulin based on daily activities does mediate depressive symptoms and glycaemic control. Further studies are required to determine whether education targeting insulin self-adjustment and diabetes management attitudes may be beneficial for glycaemic control.
ATTENUATED REGIONAL VASODILATORY EFFECTS OF GASTROINTESTINAL HORMONES IN OBESITY PRONE ANIMALS: IMPLICATIONS FOR OBESITY-RELATED HYPERTENSION

J. M.Y. How, T. J. Pumpa, D. M. Sartor

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Obese animals have reduced renal and splanchnic sympathoinhibitory responses to gut hormones that may have implications for increased vascular resistance. Our aim was to determine whether the vasodilatory effects induced by gastric leptin and cholecystokinin (CCK) are also attenuated in obesity. Male Sprague-Dawley rats were fed a medium high fat diet (MHFD; n=24) or a low fat diet (LFD; n=8) for 13 weeks. Based on weight gain, MHFD rats were stratified into obesity prone (OP; upper tertile; n=8) or obesity resistant (OR; lower tertile; n=8) groups. In isoflurane-anaesthetised rats, Doppler flow probes were attached to the renal and superior mesenteric (SM) arteries to measure vascular conductance (VC) to intravenous administration of CCK (0.1-4 µg/kg) and leptin (15 µg/kg) infusion close to the coeliac artery. OP rats had elevated arterial pressure compared to both LFD and OR rats (P<0.05 for all). CCK induced an increase in renal VC in LFD and OR rats and this was blunted in the OP rats (0.5-4 µg/kg; P<0.05 for all). OP rats had attenuated VC responses to CCK in the SM artery compared to LFD rats (1-2 µg/kg; P<0.05 for all). Leptin increased renal VC in LFD rats and this was blunted in OP rats (P<0.05). Reduced vasodilatory effects of gut hormones may contribute to elevated vascular resistance associated with obesity-related hypertension. Support NH&MRC.

IDENTIFICATION OF TARGET GENES IN OSTEOBLASTS, THE BONE FORMING CELLS, THAT ARE REGULATED DIRECTLY VIA THE ANDROGEN RECEPTOR.

P. Russell

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Background and aim: Androgens are important for bone growth and maintenance in males. Our aim was to identify target genes that are regulated by the AR in osteoblast (OBLs), the bone forming cells. To achieve this we generated a mouse model in which the AR is specifically deleted in mineralising OBLs (mOBL-ARKOs). Methods: Microarray was performed on RNA from bones of mOBL-ARKOs and controls at 6 and 12 weeks of age (n=3/group). Genes identified to be regulated by microarray were confirmed by quantitative real time PCR (n=19-20/group). Results: Microarray analysis identified 25 and 366 genes regulated by more than 1.5 fold (P <0.05) in mOBL-ARKOs at 6 and 12 weeks of age, respectively. Of these, 13 genes were regulated at both 6 and 12 weeks of age. Ingenuity analysis identified pathways and networks that were overrepresented. We used Q-pcr to confirm differential expression and found a number of genes to be regulated in the bones of mOBL-ARKOs compared to controls including genes involved in: OBL development (type 1a1 collagen (2 fold increase at 6wks (P<0.05)), osteocalcin (2.2 fold increase at 12wks (P<0.05)) Alkaline Phosphatase (2.9 fold increase at 12wks (P<0.05)); growth and development (growth hormone (3.5 fold increase at 12wks (P<0.01)), Wnt4 (2.2 fold increase at 12wks (P<0.05)), Tgfβ2 (1.9 fold increase at 12wks (P<0.05)), itibp2 (3 fold increase at 6 and 12wks (P<0.05)); and regulatory genes (Dpp4 (2.7 fold increase at 6wks (P<0.05)), adiponectin (2.5 fold increase at 12wks (P<0.02))). Conclusion: We have identified a number of target genes in mineralising osteoblasts that are directly regulated by the AR including genes known to be involved in the development and regulation of OBLs and skeletal growth. Further investigation of these AR target genes will allow us to further investigate the downstream targets of the AR in OBLs.
DELAYED CORTICAL BONE GROWTH IN MICE EXPRESSING EGFP-CRE FUSION PROTEIN UNDER THE CONTROL OF THE OSTERIX PROMOTER

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Background and Aim
The Cre/LoxP system, which enables the deletion of a gene of interest in a tissue and/or time-specific manner, has lead to significant advances of our understanding of the function of genes in a wide range of disciplines. The aim of this study was to investigate the utility of the Cre-expressing mouse line, Osx1-GFP::Cre, to investigate the hormonal control of bone.

Methods
Femur length was measured using a digital caliper. Cortical and trabecular bone parameters were determined in the femurs of Osx1-GFP::Cre mice at 6 and 12 week old by microtomography (µCT).

Results
At 6 weeks of age, Osx1-GFP::Cre mice had reduced body weight by 22% compared to wildtype controls (P<0.0001). At 6 weeks of age, Osx1-GFP::Cre mice also demonstrated delayed cortical bone growth, characterised by decreases in periosteal circumference by 7% (P<0.05) and cortical thickness by 11% (P<0.01), compared to wildtype controls. Delayed weight gain and cortical growth was overcome by 12 weeks of age, with no difference in cortical parameters observed between Osx1-GFP::Cre and wildtype controls. No differences in trabecular bone parameters (bone volume, number, thickness and separation) were observed.

Conclusion
Osx1-GFP::Cre expressing mice display a delayed growth phenotype in the absence of doxycycline treatment, evidenced by decreased cortical bone growth and body weight at 6 weeks of age. While this delay in growth is overcome by adulthood at 12 weeks of age, caution must be taken when interpreting results of skeletally immature osteoblast-specific knockout mice generated using the Osx1-GFP::Cre mouse line.

INCREASED FORMATION OF SPLANCHNIC VASCULAR ANGIOTENSIN-(1-7) FROM ANGIOTENSIN I AND ANGIOTENSIN II IS MEDIATED BY ANGIOTENSIN CONVERTING ENZYME-2 IN EXPERIMENTAL CIRRHOSIS AND PORTAL HYPERTENSION.

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2Department of Gastroenterology, Austin Health, Heidelberg, VIC, Australia

Background: Splanchnic vasodilatation plays a central role in the pathogenesis of portal hypertension. We have previously shown that mesenteric vascular angiotensin converting enzyme 2 (ACE2) expression and circulating levels of its peptide product, angiotensin-(1-7) (Ang1-7) are increased in cirrhosis. Furthermore we have demonstrated that exogenous Ang1-7 is a mesenteric vasodilator in cirrhotic rats. Aim: To examine the metabolism of angiotensin peptides in the splanchnic vasculature in cirrhosis induced by bile duct ligation in rats. Methods: Angiotensin I (Ang I) (99 pmol) or angiotensin II (Ang II) (60 pmol) were injected via superior mesenteric artery into perfused splanchnic vascular bed of cirrhotic and control rats, and Ang1-7 and Ang II levels in portal vein effluent measured by radioimmunoassay. The specific ACE2 inhibitor, MLN-4760, was added to the perfusate 15 min before the bolus dose to elucidate the contribution of ACE2. Results: In cirrhotic rats, formation of Ang1-7 from Ang II was increased almost six-fold compared to control (Area under curve (AUC) 11.94 +/- 1.91 ng/mL/s control vs 63.34 +/- 19.04 ng/mL/s cirrhotic, p =.0013). Following Ang I injection, there was no significant difference in Ang II formation (p = .2038), but Ang1-7 formation was again increased in cirrhosis (AUC 33.19 +/- 7.34 ng/mL/s control vs 82.4 +/- 28.8 ng/mL/s cirrhotic, p = .0369). Importantly, ACE2 inhibition in cirrhosis significantly reduced Ang1-7 synthesis from Ang II and from Ang I down to control levels (63.34 +/- 19.04 ng/mL/s cirrhotic vs 25.16 +/- 5.15 ng/mL/s cirrhotic with ACE2 inh, p = .0371). Conclusion: There is markedly increased formation of endogenous Ang1-7, both from Ang I and from Ang II, in cirrhosis, largely due to augmented splanchnic vascular ACE2 activity. These findings support a role for Ang1-7 and ACE2 in the pathogenesis of splanchnic vasodilation in cirrhosis.
HEPATITIS C AND CYCLOSPORINE REDUCE VIABILITY AND INDUCE APOPTOSIS IN LIVER CELLS

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2Department of Gastroenterology, Austin Hospital, Heidelberg, VIC, Australia
3Department of Infectious Diseases, Austin Hospital, Heidelberg, VIC, Australia

Severe recurrent hepatitis C (HCV) post-liver transplantation results in rapidly progressive liver fibrosis, but the underlying mechanism remains unclear. We investigated whether this might be due to enhanced hepatocyte apoptosis driven by HCV infection and the effect of immunosuppressants used. The effects of HCV infection and cyclosporine (CyA) were investigated using Huh7 cells exposed to various concentrations of CyA and/or viral constructs made using the AdEasy system containing either GFP alone (rAdGFP) or expressing the HCV structural (rAdHCV-CoreE1E2) or non-structural (rAdHCV-NS3-5B) proteins. Cell viability was evaluated using crystal violet assays. Cell apoptosis was evaluated using Western immunoblots performed on cell lysates probed for cleaved PARP. CyA at 1 mcg/mL had no effect on cell viability, but CyA at 10 and 100 mcg/mL reduced cell viability by 1.6 and 2.2 fold respectively. Infection with rAdHCV-CoreE1E2, rAdHCV-NS3-5B and co-infection with both viral constructs in the absence of CyA reduced cell viability by up to 1.6 fold. Addition of CyA at 1 mcg/mL to infection with HCV constructs reduced cell viability by 2.9, 3.1 and 5.5 fold respectively. Cyclosporine at 1 and 10 mcg/mL did not increase cleaved PARP. However, at a dose of 100 mcg/mL, cleaved PARP was increased 3.4 fold at 72 hours. Infection with rAdHCV-CoreE1E2, rAdHCV-NS3-5B and co-infection increased cleaved PARP by 1.8, 1.9 and 2.1 fold respectively at 72 hours. Addition of 1 mcg/mL CyA to HCV infections increased cleaved PARP by 1.6, 3.6, and 1.4 fold respectively at 48 hours. Addition of 10 mcg/mL CyA to HCV infections increased cleaved PARP by 2.0, 2.5 and 4 fold respectively at 48 hours. The addition of CyA to HCV infection further reduces cell viability and increases cleaved PARP compared to infection alone, indicating that CyA increases apoptosis in hepatocytes infected with HCV and may contribute to the accelerated liver disease progression post-liver transplantation.

DIFFERENT DEFINITIONS OF HCV RAPID FIBROSIS POST LIVER TRANSPLANT YIELD INSIGHTS INTO THE FIBROSIS TIMECOURSE

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2Departments of Medicine and Surgery, University of Melbourne, Melbourne, VIC, Australia
3Department of Medicine, Monash Medical Centre, Clayton, VIC, Australia

Background: Recurrence of hepatitis C (HCV) post liver transplant is universal, with a subgroup developing rapid hepatic fibrosis. Various definitions of rapid fibrosis have been used to identify risks for rapid progression, but their comparability has not been determined. This study examines risk factors for HCV-induced rapid fibrosis progression, comparing different methods of fibrosis measurement. Methods: Prospective data analysis was conducted on 131 adult patients with HCV who underwent liver transplantation. We measured year one fibrosis progression (rapid fibrosis defined as >0.4 units/year), fibrosis rate identified donor age and peak viral load, time to F2 stage fibrosis, time to cirrhosis, HCV-related graft survival, and fibrosis rate (calculated using liver biopsies graded by Metavir scoring F0-4; FR= fibrosis stage/ year post transplant). Rapid fibrosis was defined as >0.4 units/year. Variables studied included demographic, operative, immunological and post transplant event data. Results: 131 adult patients with HCV were included in the study (follow-up min 6mths, median 6.5 yrs). Multivariate analyses using F stage at 1yr revealed peak viral load (p=0.05, OR 1.01) and mean cyclosporine level (p=0.02, OR 1.01), Fibrosis rate identified donor age (p=0.02, OR 1.01) and peak viral load, time to F2 stage fibrosis identified donor age (p=0.03, OR 2.08) and non-genotype 2,3 HCV (p=0.02 OR 2.1), time to cirrhosis found CMV infection (p=0.01, OR 10.2) and HCV graft loss found peak viral load (p=0.05, OR 12.2) as significant risks for rapid fibrosis progression. Conclusion: Different methods of fibrosis measurement correlate strongly, but do not yield comparable risks. This may reflect changing relative importance of risks over time. Immunosuppression appears crucial in the first year post transplant, donor age and viral genotype perpetuate fibrosis development and CMV infection is a significant risk for cirrhosis. HCV peak viral load remains a key modifiable risk at all stages of disease.
TOLL-LIKE RECEPTOR 3 AND 7/8 FUNCTION IS IMPAIRED IN HCV PATIENTS WITH RAPID FIBROSIS PROGRESSION POST LIVER TRANSPLANTATION

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Background: Recurrence of HCV post liver transplant is universal, with a subgroup developing rapid hepatic fibrosis. Hepatitis C alters Toll-like receptor (TLR) function to evade immune clearance. Whether TLR function is related to rapid fibrosis progression remains unknown. Methods: Peripheral blood mononuclear cells from 40 HCV patients post liver transplant, 6 non-HCV post liver transplant and 7 healthy controls were stimulated with TLR subclass-specific ligands PIC (TLR3) and R848 (TLR7/8). Flow cytometry determined intracellular cytokine production and TLR expression for monocytes, NK, NKT and T cells. Rate of fibrosis progression was calculated using liver biopsies graded by Metavir scoring (F0-4; R = fibrosis stage/year post transplant). Rapid fibrosis was defined as >0.4 units/yr, dichotomized about the median observed rate (0.4). Results: IFNγ production by NK cells was lower in non-HCV post transplant than HCV patients and healthy controls (NK cells baseline p=0.01, TLR3 p=0.003, TLR7/8 p=0.02). HCV NK cells, T cells and monocytes produced more TNF at baseline and in response to TLR3 stimulation than both healthy and post transplant controls (NK cells baseline p=0.009, TLR3 p=0.0002; T cells baseline p=0.03; monocytes baseline p=0.0003, TLR3 p=0.0004). HCV monocytes produced more IL-6 at baseline (p=0.02) and in response to TLR3 stimulation (p=0.05) compared with controls. In contrast, monocytes from HCV rapid fibrosers produced less IL-6 at baseline (p=0.008) and in response to TLR3 stimulation (p=0.01) compared with slow fibrosers. NKCD56dim cells from rapid fibrosers produced less IFNγ in response to TLR7/8 stimulation than slow fibrosers (p=0.04). Conclusions: Despite immunosuppression, HCV patients have upregulated inflammatory responses to TLR stimulation compared with post transplant controls. However, rapid fibrosers have reduced IL-6 secretion by monocytes to TLR3 and reduced NKCD56dim-derived IFNγ in response to TLR7/8 stimulation. These impaired antiviral TLR responses may be an important mechanism for aggressive HCV recurrence post liver transplant.

FACTORS ASSOCIATED WITH RECURRENCE OF HEPATOCELLULAR CARCINOMA POST LIVER TRANSPLANTATION.

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Objectives: To review the outcomes of all patients transplanted at the Austin Hospital, Australia for the primary indication of hepatocellular carcinoma (HCC) between 1999 to 2011. We assessed the factors which may be associated with recurrence of HCC in the allograft comparing two groups of patients, Group A: those who were transplanted and had no recurrence and Group B: those who were transplanted but developed recurrence.

Methods: A retrospective chart based review of all patients transplanted for HCC was performed over a period of 12 years. Inclusion criteria were all adults who were transplanted at the Austin Hospital, Australia with a complete histopathological examination of their explants (N=82). The primary outcome was death from recurrence of HCC or recurrence free survival currently receiving post transplant surveillance at our centre. A multivariate analysis was performed on the patient, radiological and explant tumour characteristics listed in the table below. Multimodal therapy for HCC was classified as more than one type of therapy for HCC. Variables were expressed as median value or percentage.

Conclusion: Though the two groups were matched for patient and tumour characteristics, logistic regression analysis revealed that vascular invasion on the explant was the only statistically significant factor associated with recurrence of HCC in the allograft (p-value: 0.0072) with an OR of 12. Recurrence portended a poor prognosis with a median survival of 11 months. This study may help identify those high risk patients post transplantation who may benefit from an intensive surveillance program.
TREATMENT OF HCV IN THE SETTING OF TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA (HCC). A MISSED OPPORTUNITY?
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Objectives: HCV recurrence is universal post liver transplantation with 10% to 25% of patients developing cirrhosis within 5 years' after transplantation. We reviewed the HCV treatment history of patients transplanted at the Austin Hospital with HCC.

Methods: 44 patients who underwent liver transplantation at the Austin hospital between 1999-2011 for HCC on a background of HCV were identified from the transplant database. We reviewed their medical records both from the Austin hospital and the initial referring tertiary hospital as well as the Metavir score on the most recent allograft biopsy.

Results: 6 patients presented with HCC and were found to have HCV as their underlying cause and 3 patients were diagnosed with HCV on presentation with decompensation and subsequently found to have a HCC within 6 months. Of the remaining 36 patients who were potential candidates for HCV treatment prior to diagnosis of HCC, only 6 were treated. In these patients, the median duration of known HCV prior to HCC and therefore the treatment window was 10 years (range 1-32 years). Whilst on the wait list 8 patients were treated (CTP A: 6, CTP B: 1, CTP C: 1). 7/44 had an SVR prior to transplantation: 3 due to treatment on the wait list, and 4 due to treatment by the referring hospital prior to listing. Of the 37 patients who did not achieve an SVR, 30pts had allograft biopsies (median time 3.5yrs post transplant (range 2mnths – 9yrs) with median Metavir A2F2 (range A0-3, F0-4).

Conclusion: Despite advancements in effective antiviral therapy for HCV, rates of treatment remain poor (44%) prior to referral for liver transplantation. The diagnosis of hepatocellular carcinoma in a patient with well compensated chronic liver disease from HCV should prompt consideration for antiviral therapy to be incorporated as part of the overall treatment armamentarium with the aim of achieving SVR in the interest of preserving graft function post transplantation.

RISK STRATIFICATION OF UPPER GI BLEEDING WITH AN OESOPHAGEAL PILLCAM.
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Introduction: Emergency presentations with upper gastrointestinal bleeding are often inappropriately triaged resulting in a failure of endoscopic intervention being performed within the recommended time frame. Our aims are to investigate whether the use of PillCam ESO can differentiate between patients requiring emergency endoscopy and low risk patients who can safely wait for elective endoscopy.

Methods: A diagnostic, non-randomized, single blind (investigator), pilot study was performed at Austin Health and The Northern Hospital. 22 patients of mean age 60 years, presenting with acute GI bleeding fulfilled the inclusion criteria.

Results: Four patients presented with haematemesis and melaena, 8 with haematemesis alone and 10 with melaena alone. All patients proceeded to upper endoscopy with a mean time of 20.5hours. Capsule identified pathology in 16 patients, 9 correlated with endoscopic findings, five had a reported normal endoscopy, and two had mucosal views obscured by large amounts of fresh blood. Gastroscopy identified 10 patients who had a bleeding site. Six peptic ulcers (4 gastric/2 duodenal), 1 gastric and duodenal angioectasia, 1 oozing portal hypertensive gastropathy, 1 Mallory Weiss tear and 1 oesophageal ulceration were found. Two patients required endoscopic therapy to treat the culprit lesion. The 2 negative capsule studies with positive endoscopic findings occurred as the capsule did not reach the duodenum, the site where pathology was identified at endoscopy.

Conclusion: PillCam ESO identified all endoscopically detected pathology within the oesophagus and stomach, however failure of the capsule to reach the duodenum in a significant proportion of patients is a major limitation. In 23% the capsule study identified pathology that was not seen at endoscopy. Measures to increase the rates of duodenal visualisation are required before the Pillcam ESO can be safely utilised as a triage tool.
INCIDENTAL COLONIC UPTAKE ON PET-CT AND ENDOSCOPIC CORRELATION, THE AUSTIN EXPERIENCE.
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Introduction: Whole body $^{18}$F-fluorodeoxyglucose positron emission tomography – computed tomography (PET – CT) is a tool for the initial staging and subsequent follow up of patients with underlying malignancy. As a result incidental colonic uptake has been noted in a proportion of patients and subsequently referred to our unit for endoscopic investigation. We seek to investigate whether there is a correlation between incidental PET-CT findings and endoscopic pathology in our patient population.

Methods: A retrospective review was performed on the endoscopy database (HCNscribe) for the colonoscopy indication of positive PET-CT findings from 1st January 2004 to 17th February 2011. The endoscopy, radiology and pathology reports for each patient were then reviewed.

Results: 75 patients who had undergone colonoscopy follow up for abnormal PET findings were identified through the database. After review of the PET findings 5pts were excluded due to lack of focal uptake within the colon. 80 areas of uptake were observed in 70pts. 42 of 70pts had pathology at endoscopy with 67 polyps and 6 cancers found. Endoscopic location of these abnormalities correlated to PET hotspots in 38 of 42 pts (44polyps, 6cancers). The average size of polyps that localised to the PET site was 17.6mm compared with 4.5mm that did not localise. PET intensity initially appeared to correlate with likelihood of endoscopic colonic pathology (80% intense, 9% moderate, 9% non specific and 2% physiological uptake). However 34% of pts with intense PET scan uptake had no pathology at endoscopy and 17% of patients with colonic cancer at endoscopy had mild uptake on the PET scan.

Conclusion: Our series is the largest of its kind to date and supports the consensus that incidental colonic uptake on PET-CT should be followed up by endoscopic investigation. 60% of our patients were found to have pathology at endoscopy with 91% correlating with site on PET.

CHANGES IN TOLL-LIKE RECEPTOR 2 EXPRESSION ON PERIPHERAL IMMUNE CELLS IN CIRRHOSIS
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Background: Toll-like receptors (TLRs) are a critical component of the innate immune response. Previous reports of TLR function and expression in cirrhosis have been conflicting, involved small numbers and focused on monocytes. NK/NKT cells may also be important in innate immune responses to infection and inflammation. However, little is known about TLR changes in peripheral NK/NKT cells in advanced liver disease. Methods: Peripheral blood mononuclear cells (PBMCs) from 71 patients with Child-Pugh (C-P) A, B and C cirrhosis due to various aetiologies were collected prospectively. TLR2 and TLR4 expression was determined on monocytes, NK cells (including CD56 bright and dim subsets) and NKT cells using flow cytometry. After stimulation with TLR2 and TLR4 specific ligands, production of TNFα and IL6 by the overall PBMC population was measured by analysing cell culture supernatants using ELISA. Results: TLR2 expression on monocytes in patients with C-P C cirrhosis was significantly lower than A and B (p<0.0001). On NK cells, C-P B and C cirrhotics had significantly greater TLR2 expression compared with C-P A (p=0.0076). These changes were predominantly in the NK CD56 dim population (p=0.0052) although there was a trend to higher TLR2 expression with more advanced cirrhosis in NK CD56 bright cells (p=0.073) and NKT cells (p=0.0525). There were no significant differences noted for TLR4 expression. There were also no significant differences in cytokine production between the groups overall. The described changes were independent of the cause of liver disease. Conclusions: This study demonstrates altered TLR2 expression on monocytes and NK cell populations in C-P C cirrhosis. The monocyte findings differ from some smaller studies but may be associated with the increased incidence of gram-positive infections in cirrhosis. The NK cell changes have not previously been described and further study is warranted to determine their functional and clinical significance.
ROLE OF P21-ACTIVATED KINASE 1 IN PROLIFERATION OF COLORECTAL CANCER CELLS IN VITRO AND IN VIVO

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Background and Aim: P21-activated kinase 1 (PAK1) functions as a key node in various signalling pathways leading to cell proliferation, survival, migration and growth. PAK1 is overexpressed and activated in several human tumors including colorectal cancer (CRC), which is the second most common cause of cancer death. Hyper-activation of the Wnt signalling pathway, with concomitant effects on β-catenin function, is a hallmark of CRC. In the nucleus of CRC cells, accumulated β-catenin constitutively binds to the transcription factor TCF4, and the complex increases expression of downstream target genes and further stimulates cell proliferation and migration. The aim of this study was to investigate the importance of PAK1 in Wnt/β-catenin signalling and CRC cell proliferation both in vitro and in vivo.

Methods: PAK1 knock-down (KD) clones of the human CRC cell line DLD1 were obtained by stable transfection with shRNA targeting PAK1. Protein expression was determined by Western Blot, β-catenin/TCF4 transcriptional activities were measured by dual-luciferase assay and cell proliferation by cell counting. In the xenograft study PAK1 KD and control cells were injected subcutaneously in Scid mice.

Results: The expression of β-catenin and its downstream target gene c-myc were both lower in PAK1 KD cells compared to control cells. The β-catenin/TCF4 transcriptional activity was significantly reduced in PAK1 KD cells. Cell proliferation was also decreased in PAK1 KD cells. Tumor growth in xenograft was dramatically reduced by PAK1 KD.

Conclusion: This study has demonstrated that PAK1 is required for the expression of β-catenin and its downstream target gene c-myc, that PAK1 is important in the β-catenin/TCF4 transcriptional activity and furthermore, that PAK1 plays a crucial role in proliferation of CRC cells both in vitro and in vivo.

PROGASTRIN DERIVED PEPTIDES ARE BIOLOGICALLY ACTIVE IN VITRO AND IN VIVO

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Progastrin (PG) is a gastrointestinal (GI) peptide that is fully processed to amidated gastrin (Gamide), the major stimulant of gastric acid secretion. Several immature or unprocessed gastrins are produced by a variety of GI cancers. Immature PG forms include glycine-extended gastrin (Ggly) and the C-terminal flanking peptide (CTFP). These peptides have no effect on gastric acidity but we have shown that both Ggly and CTFP exert growth factor activities in cultured cells to increase proliferation, survival, migration, and to significantly increase proliferation in mouse colons in vivo. While Ggly is accepted as an active growth factor, there has been some debate in the literature if the biological activity of CTFP, as a 6 amino acid peptide, is specific.

Aim: Determine specificity of the biological activity of CTFP.

Methods: Using Ggly as the standard control, human (h) and mouse (m) CTFP (hSAEDEN, mSAEEDQ) were compared to mutant (hSAAAAN, mSAAAAQ) and scrambled (hENDAS, mEQAESD) peptide forms in gastric (hAGS, mMGC) and colon (hDLD-1, mMOCR) cancer cell lines. Assays used included proliferation (cell division), survival (MTT), migration (transwell) and the use of the mouse forms in gastrin knockout mice.

Results: Human and mouse CTFP both possessed growth factor activities in vitro, resulting in a significant effect not observed with the mutant or scrambled forms. In vivo, mCTFP was able to significantly increase colonic proliferation, while mutant and scrambled forms were not.

Conclusion: Using the mutant (changing charged amino acids to uncharged) and scrambled (rearranging the amino acid order) peptides demonstrated that the bioactivity of CTFP is specific to its charge and structure.
GASTRIN INCREASES ITS OWN EXPRESSION THROUGH PROXIMAL DNA ELEMENTS.

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Introduction: Gastrin increases its own synthesis in GI cancer cells via the gastrin receptor (CCK2R) through an as yet unidentified DNA response element located within the gastrin promoter.

Aim: 1. To identify the gastrin response element in the gastrin gene and
2. To determine the role of the gastrin-CCK2R positive feedback loop in the modulation of circulating gastrin in vivo in CCK2R knock-out (KO) mice.

Methods: Human gastrin promoter-deletion constructs were cloned into the pGL4 luciferase vector. Promoter activity was measured after transfection into gastric cancer cells (AGS) expressing the CCK2R. The levels of gastrin mRNA in CCK2R KO mice, which are hypergastrinemic due to decreased gastric acid production, were measured by quantitative PCR. Circulating gastrin was measured by radioimmunoassay.

Results: The activity of the pGL4-gas365 promoter construct increased 6-fold following treatment with 50nM exogenous gastrin. The responsive DNA element is within -153 and -132 bases as the activity of a construct with this sequence deleted increased by only 2.4-fold following stimulation. The gastrin mRNA in the CCK2R KO mice was 3- and 6-fold higher in the 4 and 10wk old mice, respectively, compared to wild-type C57BL/6 mice at the same age. Circulating gastrin was increased in the CCK2R KO mice compared to wild-type mice by 2.4- and 4.3-fold at 4 and 10 wks of age respectively.

Conclusion: We have shown that gastrin increases its own expression through proximal DNA elements. The CCK2R KO mice data suggest that the CCK2R is not required for the increase in gastrin mRNA or circulating gastrin in response to reduced acid secretion.

ZINC INCREASES THE EXPRESSION OF GASTRIN IN VITRO.

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Introduction: Gastrin is a gastrointestinal peptide hormone required for stimulating gastric acid secretion and maintenance of the GI mucosa. Gastrin is regulated by stomach pH, food components and other growth factors. Here we show for the first time that the transition metal zinc (Zn²⁺) has a stimulatory effect on gastrin expression.

Methods: Quantitative PCR was used to measure human gastrin mRNA in various cell lines. The effect of zinc on gastrin promoter activity was examined using a 365 fragment of the human gastrin promoter cloned into pGL4 luciferase reporter vector which was transfected into gastric cancer cells (AGS). Site-directed mutagenesis was used to mutate specific regions within the gastrin promoter. Protein expression of various signalling pathways components was determined by western blot and normalised to GAPDH expression.

Results: In AGS cells, the activity of the human gastrin promoter (pGL4-gas365) increased 6-fold and the mRNA increased 15-fold following stimulation with exogenous 50 m M Zn²⁺. Human gastrin promoter-deletion fragments identified the putative Zn²⁺ response element within the proximal promoter region -120 and -109. The zinc-finger transcription factor SP-1 is not involved in Zn²⁺-induced gastrin stimulation. Furthermore, Zn²⁺ increased gastrin promoter activity and mRNA levels via MAPK and PI3K signalling pathways. Treatment with exogenous 50 m M Zn²⁺ also increased gastrin mRNA in colorectal (50-fold) and prostate (15-fold) cancer cell lines.

Conclusion: Zinc potently increases gastrin mRNA expression in a variety of cell lines. The zinc response element was found to be within the proximal region of the gastrin promoter. The physiological role of zinc in gastrin biology remains to be determined.
PRODUCTION OF LIVER-SPECIFIC ADENO-ASSOCIATED VIRUS CARRYING ANGIOTENSIN CONVERTING ENZYME (ACE2) FOR EXPERIMENTAL GENE THERAPY IN LIVER FIBROSIS.

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Background: The renin-angiotensin-system plays a key role in the pathogenesis of liver fibrosis/cirrhosis and has stimulated major interest in the potential therapeutic role of RAS blockade in liver disease. The adeno-associated-virus (AAV) is widely used for gene therapy studies because it is non-pathogenic to both humans and animals. Therefore, the present study was undertaken to produce a liver-specific chimera AAV vector expressing ACE2 gene to investigate the effects of ACE2-over-expression in liver cirrhosis.

Methods: The mACE2 gene was inserted into a liver-specific serotype of AAV vector with enhanced green fluorescent protein (eGFP-AAV), to create mACE2-AAV and mACE2-eGFP-AAV fusion vectors. Vectors were transfected into hepatic cells Huh-7 and cultured for 48 hours. Gene and protein expressions of mACE2 were determined by quantitative real time PCR (qPCR) and western-blot. ACE2 activity assay was used to determine the proteolytic activity of mACE2 vectors. To produce large scale of AAV particles, triple-transfection in HEK293 cells was performed and the virus titre was determined by qPCR.

Results: A significant accumulation of reporter fluorescence corresponding with cycle threshold for mACE2 gene in mACE2-AAV and mACE2-eGFP-AAV transfected samples was observed at 8.23 and 9.47 respectively, but not detected in the mock sample. MACE2 protein bands were observed in both transfected samples in western-blot and no mACE2 band was observed in mock sample. Whilst high ACE2 activity level was detected in both transfected samples, mock sample didn't show any ACE2 activity. The concentrated titre of mACE2-AAV produced by triple-transfection was 4X10¹² genomic copies as determined by qPCR.

Conclusion: Both AAV-mACE2 and AAV-mACE2-eGFP were successfully cloned. Both vectors were tested positive for their ability to infect liver cells and express mACE2 using Huh-7 cells. The role of ACE2 in liver diseases will be investigated by administering mACE2 virus particles into mice with liver diseases.


IS OUR DIET AGEING US? HOW ADVANCED GLYCATION ENDPRODUCTS (AGES) WORSEN FATTY LIVER DISEASE.

This abstract has not been included at the request of the author.

TOE OR NOT TOE? THAT IS THE QUESTION IN CIRRHOTIC PATIENTS WITH VARICES.

This abstract has not been included at the request of the author.
CEREBRAL MICROHAEMORRHAGE AND BRAIN B-AMYLOID IN AGEING AND ALZHEIMER'S DISEASE

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OBJECTIVES: Incidental cerebral microhaemorrhage (MH) is frequently found in older individuals scanned with susceptibility-weighted (SWI) or gradient-recalled echo MRI.\textsuperscript{1} MH have been linked with β-amyloid (Aβ) deposition using \(^{11}\)C-PiB positron emission tomography (PET) in Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA).\textsuperscript{2} We hypothesized that Aβ deposition in asymptomatic elderly individuals is also associated with lobar microhaemorrhage (LMH).

METHODS: Cross-sectional study of 84 healthy elderly (HC), 28 with mild cognitive impairment (MCI) and 26 with probable AD who underwent 3T-SWI and \(^{11}\)C-PiB PET. \(^{11}\)C-PiB cortical binding was quantified normalized to cerebellar cortex (SUVR) and scans classified as positive (PiB+) or negative (PiB-) by visual inspection. MH were manually counted and categorized by region and as lobar or non-lobar.

RESULTS: LMH were present in 30.8% of AD, 35.7% of MCI and 19.1% of HC. The prevalence of LMH among PiB+ subjects was similar, regardless of clinical classification (AD 30.8%, MCI 38.9%, HC 41.4%, p=0.7). HC with LMH had significantly higher mean neocortical SUVR (1.7±0.5) than HC without LMH (1.3±0.3, p<0.01). In HC, there was a positive correlation between number of LMH and SUVR, and between LMH and age. In HC, PiB+ (OR 7.3, 95% CI 1.6-33.7, p=0.01) and age (OR 1.2, 95% CI 1.03-1.3, p=0.02), both independently predicted the occurrence of LMH using logistic regression.

CONCLUSION: Asymptomatic Ab deposition in older adults is strongly associated with LMH.

THE SPATIO-TEMPORAL DISTRIBUTION OF MIGRATING PERICYTES IN A RAT MODEL OF STROKE: THE EXPRESSION OF DEFINITIVE CELL MARKERS

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In ischaemic brain activated cells play an important role in reperfusion, control of blood flow, reduction of reactive oxygen species and angiogenesis. In the spontaneous hypertensive rat (SHR) stroke model, generated by temporary occlusion of the middle cerebral artery, the spatio-temporal distribution of putative migrating pericytes (smooth muscle actin-positive, αSMA+), with additional markers to confirm cell identity, was investigated. The distribution of αSMA+ cells was established using a standard immunohistochemical protocol. Positive cells for αSMA, NG2, glial acidic fibrillary protein (GFAP) and feline leukaemia virus receptor (FLVCR2) were also analysed using immunofluorescence and confocal microscopy of frozen sections. At day 3 (post-ischaemia), high densities of αSMA+ cells were located in three main regions: (A) in the medial corpus callosum, (B, less dense than A) midway through the striatum adjacent to the lateral ventricle, and (X, low density) in the peri-infarct region. By day 7, fewer αSMA+ cells remained in A & B, but increased numbers were found in Area X. By day 14 αSMA+ cells were largely concentrated in the peri-infarct area associated with blood vessels. Confocal analysis of individual αSMA+ cells demonstrated both GFAP+ and GFAP- phenotypes corresponding to astroglia and putative pericytes, respectively. At each location two morphologically distinct populations of pericytes were evident, one integrated in vessel walls and the other apparently migrating from zones of proliferation (subventricular zones) towards the infarct. FLVCR2 was expressed by the putative pericytes and a subset of the GFAP+ cells. In conclusion, putative pericytes (αSMA+, GFAP-) peak about day 7 post-ischaemia in the peri-infarct. This suggests an important role in response to ischaemia and as potential targets for pro-angiogenic therapy.
THE IBRAIN™ ANALYSIS TOOLBOX FOR SPM

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Background and Aim: We describe a free software toolbox for the SPM neuroimage analysis package that provides an automated processing pipeline for various single- or multi-subject and/or multi-session functional neuroimaging experiments.

Methods: The toolbox is written in Matlab (MathWorks, MA, USA) and is designed to work with various versions of the SPM software package (including SPM2, SPM5 and SPM8; http://www.fil.ion.ucl.ac.uk/spm/). The toolbox can optionally take advantage of the iBrain™ software package (1) to complete additional tasks. The toolbox includes an updated version of the previously released iBrain™ Laterality Toolbox (2).

Results: The pipeline includes image conversion from scanner-specific formats, pre-processing, statistical analysis, region-of-interest analysis, and display. Recent versions have proven sufficiently robust and user-friendly to be utilised routinely by research assistants and clinicians without a computing or physics background. Paradigms in which the scripts have been successfully utilised include block-design (e.g. 3), event-related (e.g. 4), simultaneous EEG/fMRI (e.g. 5) and functional connectivity (e.g. 6). The toolbox was recently used in a randomised trial (7) to analyse multi-subject multi-session fMRI data consisting of 305 fMRI sessions. The design and subject data were specified and then the toolbox generated results for all sessions without further user intervention.

Conclusions: The iBrain™ Analysis Toolbox for SPM is a useful addition to the SPM and iBrain™ neuroimaging analysis packages. We use the toolbox routinely, and in July 2011 we made it available to all under the GNU General Public License at http://www.brain.org.au/software/.

STROKE RESEARCH AT THE AUSTIN HOSPITAL: OUTSTANDING RECRUITMENT INTO THE AVERT TRIAL.
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Aim: A Very Early Rehabilitation Trial (AVERT) is a large, investigator led, multi-centre, phase III randomised controlled trial of very early rehabilitation (with a focus on mobility) after stroke. The Austin Hospital stroke unit team aims to recruit 10% of stroke admissions into the trial. Method: The inclusion and exclusion criteria are broad but patients must be admitted and recruited within 24 hrs of stroke symptoms. A team of nurses and physiotherapists are trained to assess patients, deliver and record rehabilitation interventions. All outcomes are blinded, with disability at 3 months (modified Rankin Scale) the primary outcome. Recruitment of 2104 patients will provide 80% power to detect a significant effect (2 sided, \( p = 0.05 \)). Results: The Austin Hospital commenced recruitment in July 2006, the first of 35 hospitals. Over five years, three main investigators and more than 40 hospital staff have supported this trial. 1688 stroke patients were screened for eligibility, with 192 patients recruited (11.4%). At 3 months, 181 patients have completed the 3 month follow-up with 21 deaths and 1 dropout. The hospital has recruited the largest number of patients to the trial, contributing 18% of the 1041 patients recruited. Conclusion: The Austin Hospital is the flagship hospital for this trial, with the stroke unit team achieving trial recruitment goals as well as recruiting the largest number of stroke patients into the AVERT trial. The sustained commitment of staff to clinical research over 5 years is making a major contribution to this important international clinical trial.

MODULATION OF CONDITIONED FEAR BY RELAXIN-3/RXFP3 SIGNALLING IN THE CENTRAL AMYGDALA OF THE RAT
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Relaxin-3 (RLN3) is enriched in GABAergic neurons of the nucleus incertus, which are activated by stress and corticotropin-releasing factor (CRF). Relaxin-3 neurons innervate areas containing high densities of RLN3 receptor, RXFP3. The central amygdala (CeA), a region involved in fear, is encapsulated by RLN3 terminals and contains many CRF neurons. We investigated effects of RLN3/RXFP3 signaling on fear memory and extinction following bilateral intra-CeA infusions of RXFP3 agonist (R3/I5) or antagonist (D-R3/I5). Male Sprague-Dawley rats (14-16/group) were fear conditioned to tone-footshock pairings, extinction trained, and extinction tested on successive days. Rats infused with agonist R3/I5 (40 pmol/0.2 µl aCSF) prior to extinction training, displayed less freezing compared to control rats. In the extinction test, rats infused with R3/I5 also displayed less freezing. Rats infused with R3/I5 immediately after extinction training, also displayed less freezing in the extinction test (>90% less). These data suggest RXFP3 activation in CeA impaired fear recall and enhanced consolidation of extinction memory. Rats infused with antagonist D-R3/I5 (80 pmol/0.2 µl aCSF) prior to conditioning, displayed less freezing during extinction training and testing. CeA infusion of D-R3/I5 immediately prior to extinction training had no effect on subsequent freezing. This suggests that RXFP3 antagonism before fear acquisition impaired fear memory, but not acquisition, and antagonism of RXFP3 prior to extinction had no effect on recall and extinction. This suggests a role for RLN3/RXFP3 in fear memory and extinction. We recorded from nucleus incertus neurons and tested their response to intracerebroventricular CRF (3 µg), followed by juxtacellular labeling. Neurons were activated (n=23, 3.2±1.3 to 7.2±2.1 Hz), inhibited (n=16, 4.5±1.3 to 1.9±1.1 Hz) or unaffected (n=11) by CRF. Juxtacellular labeling revealed most activated neurons were RLN3-positive (9 of 11) whereas inhibited neurons were all RLN3-negative. Further studies will investigate the role of CRF activation of this system.
A NOVEL NOX INHIBITOR (VAS2870) PROVIDES NEUROPROTECTION OF HUMAN NEURONS

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Background: Stroke is the second leading cause of death worldwide. Almost 90% of stroke patients are excluded from common thrombolysis therapy. There is a need for translatable mechanisms of neuroprotection in stroke. Oxidative stress plays an active role in stroke-induced injury. NADPH oxidase (NOX) is a major source of oxidative stress and therefore could be an effective therapeutic target in stroke. VAS2870 is a novel NOX inhibitor, which significantly improved neurological function in both in vivo and in vitro animal studies. Its effects have not yet been shown on human tissue. Here we demonstrate the effects of VAS2870 on human neurons derived from human embryonic stem cells (ESCs). Methods: Human ESCs were differentiated into neurons in the presence of the bone morphogenic inhibitor protein, Noggin. The mature neurons were maintained for 11 days prior to the induction of injury. Two different injury models were used: oxygen glucose deprivation (OGD) and H₂O₂ mediated oxidative stress. 10 µM, 20 µM and 50 µM concentrations of VAS2870 were added at the time of injury. Cell death was analysed using the lactate dehydrogenase assay. Results: VAS2870 shows neuroprotection at 20 µM and 50 µM concentration in both injury models. The highest reduction of neuronal cell death was observed at 50 µM (33% following OGD injury and 67% following of oxidative stress). Conclusion: We have shown that neuroprotection in human tissue is similar to animal models and we believe that VAS2870 or inhibitors more specific to individual NOX isoforms have a potential to be a therapeutic for stroke.

NEUROANATOMICAL CHANGES IN ROLANDIC EPILEPSY ASSESSED USING MORPHOMETRIC ANALYSIS OF STRUCTURAL MRI

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Rolandic epilepsy is one of the most common focal electroclinical epilepsy syndromes occurring in childhood. Distinctive features of Rolandic epilepsy include its specific EEG signature, seizure semiology, and age at onset, in an otherwise developmentally normal child. We use cortical thickness analysis of high resolution whole-brain MRI to investigate subtle regional structural variations in brains of children with Rolandic epilepsy. These analyses may reveal structural correlates of the functional changes that define this disorder. Methods: Nine Rolandic epilepsy subjects (mean age 15.8 ± 2.3 years) and 32 neurologically normal controls (mean age 16.8 ± 4 years) were included in the study. Subjects were imaged on a Siemens Sonata 1.5 T MRI scanner using a coronal T1-weighted whole-brain MPRAGE acquisition. MRI scans were processed using the default FreeSurfer processing stream (http://surfer.nmr.mgh.harvard.edu/, version 5.0). Vertex-wise comparisons between Rolandic epilepsy subjects and controls were undertaken, including age as a covariate of no interest in the statistical model. The mean cortical thickness difference was estimated at vertices in which there was a significant difference. Results: Bilateral cortical gray matter thickness increases were observed. The most significant increases in gray matter thickness were primarily located in the frontal lobe. Specific areas of increase included the middle frontal gyrus, Brocas area and the supramarginal gyrus. More diffuse regional thickness increases were observed in the parietal lobe bilaterally. A small region of decreased cortical thickness was identified in the right postcentral sulcus. Comparison of the cortical thickness in these regions suggested that the abnormality manifests as an average increase of 0.41 mm in the Rolandic epilepsy cohort. Conclusions: The presence of subtle cortical thickening in Rolandic epilepsy patients may be interpreted as mild regional dysplasia. This points towards an altered neurodevelopmental pathway in Rolandic epilepsy patients, which may be part of the pathophysiology of this form of epilepsy.
CHANGES TO THE CORTICAL SINGING NETWORK FOLLOWING RIGHT ANTERIOR TEMPORAL LOBECTOMY


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This study arose in the context of having to estimate risk to the music abilities of a trained singer (case AM) undergoing right anterior temporal lobectomy (RATL) for medically intractable epilepsy. To date there has been no systematic investigation of the reorganization of music function in the presence of epileptogenic lesions, although it is well established that RATL can impair pitch and melody discrimination and pitch working memory in nonmusicians. Using fMRI, we compared the cortical network activated by covert singing with lyrics before and after surgery, while taking language activation and singing expertise into account. Before surgery, AM showed lower than expected pitch accuracy for someone of her singing experience, thus we compared her to 12 healthy controls matched for pitch accuracy of singing. AM showed an atypical pattern of activation before surgery, characterized by partial activation of the nonexpert singing network and diffuse activation of association cortex typical of generalized cortical hyperexcitability in intractable epilepsy. After surgery, there was evidence of significant cortical network change (p < 0.05, corrected), with elimination of association cortex activation producing a more focal profile similar to nonexperts. These changes coincided with a significant increase in AM's pitch accuracy of singing after surgery relative to controls (t(11) = -2.578, p = 0.026), accompanied by the subjective experience of being a more technical and less emotionally based singer. Our findings demonstrate a cortical basis for improved cognitive performance following efficacious epilepsy surgery, and point to reorganization of music function in patients with epileptogenic lesions.

IMPLANTED RAT NEUROEPITHELIAL CELLS PROMOTE SCARRING IN THE INJURED RAT SPINAL CORD

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Spinal cord injury results in the loss of both sensory and motor function within the central nervous system (CNS). The mammalian CNS does not have the ability to regenerate axons therefore spinal cord damage is both devastating and permanent. Research suggests embryonic spinal cords cells, known as Neuroepithelial cells (NE), may have the potential to stimulate injured axons and encourage growth after injury. Aim: to examine the growth promoting potential of NE cells after adult rat spinal cord injury. Methods: Rat NE cells were dissected from E11.5 embryos, dissociated and implanted into an adult rat spinal hemi-section injury (n=8). Six weeks after injury rats received cortical injections of Biotin Dextran, to label corticospinal tract motor axons. Two weeks after tracing, rats were sacrificed and perfused fixed. Immunohistochemistry was performed for Avidin Peroxidase and counterstained with cresyl violet to visualise sprouting axons within the implant site. Results: Results show a significant difference in spinal cord volume between treatment and control groups. There is also a significant difference in volume between control and NE implant sham groups. These results suggest that NE cells have an uncontrolled growth potential and without sufficient guidance promote significant scarring within the spinal cord in both injured and non injured animals. Paradoxically, results also suggest NE cells have the ability to form neural pockets, resulting in a positive effect on axonal outgrowth. Conclusion: Cellular phenotype is critical when implanting embryonic tissues. A neural phenotype strongly promotes growth while a scarring phenotype is inhibitory.
FUNCTIONAL CONNECTIVITY OF THE THALAMUS IS REDUCED IN CHILDHOOD ABSENCE EPILEPSY

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Introduction: Genetic generalised epilepsy (GGE) is characterised by episodic brain dysfunction involving widespread hypersynchronous activity appearing as generalised spike wave (GSW) discharges on the EEG. The network of brain regions that are active at the time of these events have been defined using EEG-fMRI. In addition to these paroxysmal events, GGE patients also show increased cortical excitability and mild ongoing cognitive impairments, which suggests that the activity and function of brain networks may also be affected during the baseline state between GSW events. Functional connectivity describes the relationship between different regions of the brain that network together to perform a common function. In this study we hypothesised that functional connectivity would be altered in GGE, due to the presumed disturbance in network activity and function in these patients. To test this hypothesis, we acquired resting-state fMRI in a cohort of eleven patients with untreated childhood absence epilepsy (CAE) and measured functional connectivity using a whole-brain voxel-wise analysis. We performed a group comparison with eleven healthy controls in order to identify regions of altered functional connectivity. Results: The averaged connectivity map for the control group showed high numbers of connections in the thalamus and basal ganglia. In contrast, the average CAE map showed the greatest number of functional connections in the cortex whilst sub-cortical structures had relatively fewer connections. Statistical comparison revealed significant group differences bilaterally in the thalamus and cortex. Our observation of functional connectivity abnormalities in a resting-state free from GSW activity suggests an enduring change in sub-cortical and cortical functional networks as part of the underlying pathophysiology of CAE.

MEASURING ATTENTIONAL FUNCTION IN ACUTE STROKE TELLS US SOMETHING MEANINGFUL

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Background The viability and usefulness of cognitive assessment in acute stroke has been questioned. Practical challenges arise from focal neurological deficits and heterogeneity in arousal state.

Aim To test the feasibility of assessing attentional function in acute stroke and to evaluate whether acute measures of attention correlate with attentional function at 3 months.

Method Patients with confirmed stroke completed 2 computerised cognitive tasks (CogState) within 2 weeks of stroke and again at 3 months post-stroke. The tasks were a simple reaction time task (detection) and a choice reaction time task (identification) that required a button press to visual stimuli (playing cards). Each task took approximately 4 minutes. The Montreal Cognitive Assessment (MoCA) and an extended neuropsychological battery were also administered at 3 months.

Results Thirty-three patients (mean age 75.5 years, SD 11.9) participated. The majority showed increased detection and identification speed from baseline to 3 months, although 2 patients did exhibit a substantial decrease in speed. Correlations revealed that both detection speed \(r = -0.73, p < .001\) and identification speed \(r = -0.61, p = .007\) at baseline were associated with attentional function at 3 months, as measured by established neuropsychological tests ( Trails-A, Digit span, Digit symbol). In addition, detection speed at baseline was correlated with total 3-month MoCA score \(r = -0.54, p = .012\).

Conclusion Simple and brief computerised assessment of attentional function in acute stroke is feasible and shows a clear relationship with longer term attentional and cognitive performance.

CLINICAL GENETIC STUDIES IN BENIGN CHILDHOOD EPILEPSY WITH CENTROTEMPORAL SPIKES (BECTS)

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GENETICS OF TEMPORAL LOBE EPILEPSY AND HIPPOCAMPAL SCLEROSIS (TLE+HS): PRELIMINARY RESULTS:

This abstract has not been included at the request of the author.
Diffusion MRI tractography allows the complex structural connectivity of the brain to be estimated in vivo. As the methodologies for analysing these data become more sophisticated, it is vital that the tractography data itself be as robust and biologically-accurate as possible. Here we propose a modular improvement to common streamlines tractography variants by incorporating prior information about tissue types within the brain into the streamlines process. The framework begins with correction of susceptibility-induced distortions in the diffusion-weighted images, such that correct alignment with the reference anatomical image can be achieved using a simple rigid body registration. The anatomical image is segmented into the three principal tissue types - grey matter, white matter and cerebro-spinal fluid - using freely-available software. This information is then used during tractography to influence the termination of the tracks generated; they are constrained to connect spatially-distant areas of grey matter by traversing the white matter. Fibres abruptly terminating in the white matter or entering fluid-filled regions are rejected as spurious. Preliminary results of tractography using this framework compared to conventional tractography indicate a reduction of false positive connections. Maps indicating the density and terminations of fibres appear much more biologically plausible, provided state-of-the-art models of diffusion and tractography algorithms are used. It is proposed that this framework is a worthwhile improvement to diffusion MRI tractography, which can be implemented with a minimal increase in acquisition time, and should benefit all tractography analysis methods currently being employed.
KUFS DISEASE, THE MAJOR ADULT FORM OF NEURONAL CEROID LIPOFUSCINOSIS (NCL), CAUSED BY MUTATIONS IN CLN6

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The molecular basis of Kufs disease is unknown, whereas a series of genes accounting for most of the childhood onset forms of neuronal ceroid lipofuscinosis (NCL) have been identified. Diagnosis of Kufs disease is difficult because the characteristic lipopigment is largely confined to neurons and may require brain biopsy or autopsy for final diagnosis. We mapped 4 families with Kufs disease where there was good evidence for autosomal recessive inheritance, and found two peaks on chromosome 15. Three of the families had type A Kufs disease (presenting with progressive myoclonus epilepsy) and one had type B (presenting with dementia and motor system features). Sequencing of a candidate gene in one peak shared by all four families revealed pathogenic mutations in all three. We subsequently sequenced CLN6 in eight other families, three with recessive type A Kufs disease. Mutations in both CLN6 alleles were found in the three type A cases and in one family with unclassified Kufs disease. Mutations in CLN6 are the major cause of recessive type A Kufs disease. The phenotypic differences between variant late infantile NCL, previously found to be caused by CLN6, and type A Kufs disease are striking with a much later age of onset and lack of visual involvement in the latter. Sequencing of CLN6 will provide a simple diagnostic strategy in this disorder where definitive identification usually requires invasive biopsy.
DISCOVERY OF A NOVEL GENE FOR EPILEPSY BY MASSIVE PARALLEL SEQUENCING IN A SINGLE SUBJECT.


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Aim: We sought to discover the cause of progressive myoclonus epilepsy in an Australian woman whose parents were second cousins. All known causes had been excluded and we applied the power of new genetic technologies to attempt this. Method: Linkage analysis was performed using SNP chips in the patient, her healthy brother and 2 unaffected parents. Following identification of a single linked region, massive parallel sequencing was performed to identify the molecular defect. Results: Linkage analysis identified a single peak on chromosome 17 containing 251 genes. Massive parallel sequencing revealed 3 unique exonic variants present in the homozygous state in the linked region. Two were biologically implausible and a mutation in GOSR2, a gene encoding a protein not previously associated with disease, remained. The patient had an unusual phenotype with onset of ataxia at age 2, subsequent development of myoclonus epilepsy and the association with scoliosis and a raised creatine kinase. From a database of unsolved patients with progressive myoclonus epilepsy we identified 4 other cases with a similar phenotype that all proved to have exactly the same mutation. GOSR2 encodes a protein involved in processing of proteins in the Golgi apparatus and the mutation results in mislocalization of the protein product. Conclusion: We have identified a novel clinico-molecular syndrome causing progressive myoclonus epilepsy, scoliosis and elevated creatine kinase. Rapid diagnosis is now possible using molecular methods. This study illustrates the power of the new molecular genetic techniques to discover a novel gene in even a single case.

FAMILIAL EPILEPSIES IN ISRAEL: A CLINICAL AND MOLECULAR GENETIC STUDY OF 211 FAMILIES


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Aim: Discovering the genetic basis of the common epilepsies is a major priority in epilepsy research. To determine the generalizability of our findings in our Australian cohort we collected families from the ethnically heterogeneous population of Israel over 12 years and intensively studied them to determine their classification and molecular lesion. Methods: Following referral to the project, individuals were classified into epilepsy syndromes. Familial epilepsy classification was possible following the successful classification of at least two family members. Pedigrees were analysed and molecular genetic studies were performed as appropriate. Results: 211 families were studied. We successfully classified 171 families into broad familial epilepsy syndrome groups; 88 Generalized, 22 Focal, 29 Mixed and 32 Special. 40 families remained unclassified. Arab families made up 25% of our cohort with the remaining families Jewish (44% Sephardic, 23% Ashkenazi, 8% mixed Jewish). Arab families were disproportionately represented in our Special familial syndrome group and were more likely to be consanguineous. Molecular lesions were identified in 34/211 families (16%) including three novel epilepsy findings. Nine novel epilepsy syndromes were identified and clinically characterized. Conclusions: The findings in our Israeli cohort were generally reflective of those made in our Australian families. 81% of families were successfully classified and causative mutations were identified in no less than 16% of the total cohort. In addition, however, 12 novel clinical and/or molecular genetic discoveries were made of which many remain unique to our Israeli cohort highlighting the value of genetic studies in distinctive populations.
THE UTILITY OF 11CPIB–PET FOLLOWING ACUTE ISCHAEMIC STROKE.

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Background: Stroke increases the risk of cognitive impairment1. The mechanism remains uncertain. Alzheimer’s disease (AD) and Vascular Cognitive Impairment (VCI) are the commonest forms of cognitive impairment. They share risk factors and have considerable clinical and pathological overlap2. There is evidence that vascular pathology may have a causative and additive effect on amyloid deposition3, the pathological hallmark of AD. Using 11CPIB-PET enables assessment of amyloid deposition3. We hypothesised that an acute ischemic stroke may trigger amyloid deposition and cause increased 11CPIB retention.

Method: Eligible patients admitted with stroke underwent an MRI scan to determine stroke characteristics and for anatomical co-registration. This was followed by an 11CPIB-PET scan within 21 days of the stroke. Repeat scans were performed at intervals ranging from 2 weeks to one year where possible. Analysis of scans was based on standard uptake value ratio (SUVR) of regions of interest using the cerebellar cortex as reference region. A ratio exceeding 1.4 was considered high.

Results: 50 patients underwent PET scans. 34 were male; mean age was 69.9 years (range 42-87). On initial scan 16 patients showed high PiB retention in the region of the stroke. 15 of these patients showed varying degrees of haemorrhagic transformation in the same region. Follow-up scans in 7 of the patients who initially showed retention of 11CPIB were negative. Follow up scans were also performed in 9 patients whose initial scan was normal. The repeat scans showed no significant change compared to baseline.

Conclusion: After acute ischaemic stroke there may be focal increase in 11CPIB retention. The normalisation of the phenomenon on repeat scan suggests that this was likely due to extravasation of 11CPIB secondary to reduced blood brain barrier integrity or some other inflammatory response. It is unlikely that the retention indicates the presence of amyloid.

References:
LANGUAGE FUNCTIONAL CONNECTIVITY APPEARS MINIMALLY DISRUPTED IN BENIGN EPILEPSY WITH CENTRO-TEMPORAL SPIKES

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Aim: Benign epilepsy with centrotemporal spikes (BECTS) is a common childhood epilepsy syndrome with active interictal epileptiform discharges, but a generally good prognosis. We have previously documented subtle language deficits in BECTS. Task-based functional magnetic resonance imaging (fMRI) displayed language activation to be less 'left-lateralised' in anterior language regions, whilst neuropsychology testing revealed impaired language performance. Our aim was to investigate whether there are abnormalities in language system network activity in BECTS patients during the resting-state.

Methods: Twenty-six BECTS patients and 15 age-matched controls underwent two fMRI sessions - a language activation study (orthographic lexical retrieval task) and a resting-state study. The resting-state study utilized a seeded functional connectivity (FC) method of the left middle frontal gyrus (LMFG) to reveal co-fluctuating regions of the language network. Two different FC approaches were used to investigate the language network: (1) using previously published language seed coordinates from a sample of healthy adult participants; and (2) using subject-specific seed coordinates, based upon each individual's results from their fMRI language activation study. This analysis was restricted to participants who had successfully completed both fMRI studies (17 BECTS, 15 controls). Individual functional connectivity maps were generated and then combined in a second level, random effects analysis to test for differences between groups.

Results: Both FC approaches showed typical patterns of language activation in the BECTS and control participants. Results from the first seed selection method revealed no significant difference in language activation between the groups in any region. This result was also reflected in the second seed selection method, with no significant difference displayed in connectivity between the groups in the language network.

Conclusions: We found no significant disruption of the resting-state language network in BECTS children. This suggests that if resting-state language connectivity is disrupted in BECTS, the change is likely to be subtle.

GENETICS OF SYNCOPE: A TWIN STUDY

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Aim: Syncope is defined as a sudden transient loss of consciousness due to cerebral hypoperfusion with spontaneous recovery. Vasovagal syncope (VVS) is the most common form of syncope. A possible genetic basis of VVS has been suggested but the evidence is not very strong. We performed a twin study to clarify this. Method: Twin pairs were recruited through the Australian Twin Registry (50 pairs) and through our syncope family studies (1 pair), then interviewed using a standardized syncope questionnaire. Casewise concordance rates of the Monozygotic (MZ) and Dizygotic (DZ) twins were compared. The family history of concordant MZ twin pairs was investigated. Results: Concordance for syncope was higher in MZ (0.75) than DZ twins (0.50) (p=0.061). A significant difference was found for twins who fainted at least twice without external triggers (MZ=0.71 vs. DZ=0.27, p=0.018). Similarly, concordance of syncope associated with typical vasovagal triggers (blood, injury, medical procedures, pain, frightening thoughts, prolonged standing) was significantly higher in MZ (0.62) than DZ (0.00) twins (p<0.001). Twelve of 19 concordant MZ twin pairs reported sparse or no other affected family members, suggesting complex inheritance. There was denser family history in the remaining 7 pairs consistent with either complex or autosomal dominant inheritance. Conclusion: Our data strongly supports the relevance of genetic factors in VVS and suggests that most cases follow complex inheritance.
RARE COPY NUMBER VARIANTS ARE AN IMPORTANT CAUSE OF EPILEPTIC ENCEPHALOPATHIES


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Aim: Rare copy number variants (CNVs) – deletions and duplications – have recently been established as important risk factors for both generalized and focal epilepsies. We aimed to systematically assess the role of CNVs in epileptic encephalopathies, the most devastating and often etiologically obscure, group of epilepsies.

Method: We evaluated 315 patients with epileptic encephalopathies characterized by epilepsy and progressive cognitive impairment for rare CNVs using a high-density, exon-focused whole-genome oligonucleotide array.

Results: We found that 25/315 (7.9%) of our patients carried rare CNVs that may contribute to their phenotype, with at least half being clearly or likely pathogenic. We identified two patients with overlapping deletions at 7q21 and two patients with identical duplications of 16p11.2. In our cohort, large deletions were enriched in affected individuals compared to controls, and four patients harbored two rare CNVs. We screened two novel candidate genes found within the rare CNVs in our cohort but found no mutations in our patients with epileptic encephalopathies. We highlight several additional novel candidate genes located in CNV regions.

Conclusion: Our data are the first to highlight the significance of rare copy number variants in the epileptic encephalopathies and show that CNV analysis should become a routine clinical test for these patients. Our findings also highlight novel candidate genes for further study.
SUPER-RESOLUTION TRACK-DENSITY IMAGING STUDIES OF MOUSE BRAIN: COMPARISON TO HISTOLOGY

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Introduction: Our recently proposed track-density imaging (TDI) technique was introduced as a means to achieve super-resolution using diffusion MRI. This technique can increase the spatial resolution of the reconstructed images far beyond the acquired MRI resolution by incorporating information from whole-brain fibre-tracking results. In addition, it also provides very high anatomical contrast with a new MRI contrast mechanism. However, the anatomical information-content of this novel contrast mechanism has not yet been validated.

Methods: In this work, we use diffusion MRI of ex vivo mouse brains acquired at 16.4T, to compare the results of the super-resolution TDI technique with histological staining (myelin and Nissl stains) in the same brains. Furthermore, a modified version of the directionally-encoded colour TDI map is introduced, which reduces the TDI intensity dynamic range, and therefore enhances the directionality colour-contrast.

Results: Good agreement was observed between structures visualised in the super-resolution TDI maps (20µm resolution; i.e. a factor of 125 increase over acquired image resolution) and in the histological sections, supporting the anatomical information-content of the images generated using the TDI technique.

Discussion: The results show that the TDI methodology does provide meaningful and rich anatomical contrast, in addition to achieving super-resolution. Furthermore, this study is the first to show the application of TDI to mouse brain imaging: the high-resolution, high-quality images demonstrate the useful complementary information that can be achieved using super-resolution TDI.

IDENTIFYING NOVEL AUTISM GENES IN A LARGE MULTIPLEX FAMILY

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Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that are characterised by impairments in language and social interaction. ASDs have a strong genetic basis with studies showing up to 90% heritability. Up to 20% of relatives of children with ASD have the “broader autism phenotype” (BAP) characterised by less severe deficits in communication, social interaction and stereotyped behaviour. Aim: This study aims to clinically phenotype a large multiplex family with multiple affected members with ASD and the BAP in order to use this family for linkage analysis to identify novel ASD genes of major dominant effect. Method: In this study we phenotyped family W using multiple standardized measures and a semi-structured interview with novel tasks. Phenotypic patterns were scrutinized to determine affected status. 22 individuals were genotyped and parametric linkage analysis was carried out. Results: There were 6 individuals with ASD and 14 with BAP. Linkage analysis mapped ASD traits to a single region: chr7q21.11-7q21.3 with a parametric LOD score of 3.19. Haplotype analysis showed that the disease segregated with 15/17 affected individuals. Conclusion: The high LOD score and identification of segregating haplotypes in this family suggests that a gene of major dominant effect lies in the chr7q21.11-7q21.3 region. We plan to progress to targeted next generation sequencing to find the causative variant.
CASE OF SYNDROME OF HEADACHE WITH NEUROLOGICAL DEFICITS AND CEREBROSPINAL FLUID LYMPHOCYTOSIS (HANDL) WITH FOCAL SLOWING ON ELECTROENCEPHALOGRAM

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We describe a case of headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL) in a patient presenting with a three-week history of recurrent severe headaches associated with negative sensory symptoms and dysphasia. The patient had no cardiovascular risk factors and no family history of migraines. Neurological examination was unremarkable. Cerebral magnetic resonance imaging was unremarkable. Cerebrospinal fluid (CSF) analysis revealed lymphocytosis (leucocytes 84 x 10⁶/L, 100% lymphocytes).

Extensive laboratory investigations of CSF and serum did not reveal an infectious, autoimmune, or metabolic cause. Visual evoked potentials were normal. Awake electroencephalogram revealed intermittent 3 to 5 Hz generalised slowing and frontal intermittent rhythmic delta activity (FIRDA), without epileptiform discharges. Repeat CSF analysis showed marked reduction of the total leucocyte count and remained negative for infectious aetiology. Propranolol was commenced and no recurrence of headache or neurological symptoms was observed at follow-up. A review of the literature on the topic is discussed.

USE OF A RAT MODEL OF ISCHEMIC STROKE TO IDENTIFY MARKERS OF STROKE PROGRESSION

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Aim: Stroke is the third most common cause of death and a major cause of disability. Diagnosis and management of stroke is limited by the lack of rapid diagnostic assays for use in an emergency setting. Currently, only one thrombolytic drug is available for stroke patients. However, its use is limited as stroke onset time needs to be identified for successful treatment within the time limit. Identification of appropriate biological markers could expand the proportion of patients eligible for existing therapy. We aim to analyse the expression profile of molecules in the blood during the acute phase after experimental stroke in hypertensive animals. We intend to establish a biological “stroke clock” of blood biomarkers by identifying those showing changes over time. Methods: Stroke was induced by thread occlusion of the middle cerebral artery in male hypertensive rats followed by reperfusion 1.5 hours later. Blood samples were taken over 24 hours post-stroke. Blood RNA was isolated and analysed by microarray or sequencing for molecules showing expression profiles of interest. Results: Pilot data analysed by microarray enabled identification of many genes showing significant changes in expression levels. Analysis of the current experiments is in progress and will be used to expand this data. Conclusion: These results validate the use of gene expression profiles to monitor stroke progression. This approach could enable identification of a single set or multiple sets of biomarkers for use in an acute setting to ascertain time of stroke onset and facilitate the safe use of current therapies.
LIMITATIONS OF FIBRE TRACKING FOR THE PURPOSE OF NEUROSURGERY: A SYSTEMATIC STUDY

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Introduction: This study aims to systematically investigate the limitations of utilising the tensor-based methods (DTI) [1] for the purpose of delineating white matter fibre tracts of neurosurgical interest, such as the cortico-spinal tracts, and secondly to compare the tensor-based tractography results to those obtained using our tractography method, known as Constrained Spherical Deconvolution (CSD) [2].

Methods: Diffusion-weighted data were acquired on 45 healthy controls using a 3T Siemens Trio. Each data set was analysed using a DTI-based method in conjunction with both deterministic and probabilistic tracking algorithms [3] and also with a CSD based method combined with a probabilistic tracking algorithm. Tractography analysis was systematically performed in each subject’s own space using co-registered regions of interest (ROI) identified from a template of the motor cortex.

Results: All DTI tractography results (both deterministic and probabilistic based methods) substantially underestimated the extent of tracks within the motor cortex, in all subjects. The CSD-based tractography method combined with a probabilistic tracking algorithm consistently produced fibre tracks extending throughout the entire motor cortex.

Discussion: Tracking using DTI-based methods routinely failed to delineate more than a narrow subset of the known extent of the motor tracts. Failure of the DTI-based methods is most likely due to the tensor model being unable to represent the constituent fibre populations in voxels containing crossing fibres [4, 5]. Such regions are known to be widespread [6]. These findings demonstrate that tensor-based tractography results may be extremely unreliable in clinical practice. This issue is of immediate clinical concern because there is increasing interest from surgeons to utilise readily available DTI-based tractography techniques for the purpose of neuro-surgical navigation. In contrast, the CSD-based methodology consistently demonstrated fibre tracks extending throughout the entire motor cortex in all subjects. These promising results suggest future clinical applications may now be feasible.

LOW ACTIVITY LEVELS AFTER STROKE LIKELY CONTRIBUTES TO POOR SKELETAL AND METABOLIC OUTCOMES IN STROKE PATIENTS. PROFILE OF PATIENTS ADMITTED FOR STROKE AT AUSTIN HEALTH

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Background: Poststroke bone loss is pronounced [1], contributing to increased fracture risk [2]. Many stroke patients also experience insulin resistance [3]. The emergence of these health issues are unknown but physical activity can maintain or improve bone mineral density (BMD) [4] and insulin sensitivity [5] in chronic stroke patients, and may be of benefit in the acute stroke period. Aims: To determine the skeletal and metabolic profile of non-diabetic stroke patients who are moderately impaired, early after stroke, with the intent of following patients prospectively to report the emergence of these skeletal and metabolic changes. Methods: From March 2010-June 2011, 938 stroke unit patients were screened. Only medically stable, non-diabetic patients without history of stroke, who had hemispheric stroke and were unable to walk within the first week of stroke (n=29) were approached, of whom 19 consented and were assessed within 2-weeks of stroke. Outcome measurements of interest were: total body BMD, and body composition using DXA; glucose tolerance (GTT); and physical activity monitoring (accelerometry). Results: Patients were 42% female (n=8), with median age 69.4 years (range 41.7 – 89.8). BMD was normal in 52.6% (n=10), osteopenic in 31.5% (n=6) while 5.3% (n=1) were osteoporotic. Glucose tolerance was tested in non-dysphagic patients (n=11, 58%). Results indicated 36% (n=4) had normal glucose tolerance, 45% (n=5) had impaired glucose tolerance, and 18% (n=2) exhibited a diabetic response. Physical activity was low. Median number of positional changes was 33 (range 2-133) from 8am-5pm, with 24.5 minutes spent upright (range 0-152). BMD and glucose tolerance profiles were similar to the Australian population [6,7]. Conclusion: Despite relatively low risk profiles, risk of fractures and diabetes escalates in stroke patients and in part may be contributed to by the low activity levels demonstrated immediately after stroke. Early exercise interventions may alleviate some of these detrimental changes.

(6) Australian Institute of Health and Welfare, A snapshot of osteoporosis in Australia 2011
A COMPARISON OF FUNCTIONAL OUTCOMES FOLLOWING THROMBOLYSIS THERAPY IN STROKE PATIENTS AGED 80 OR ABOVE

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Introduction: Thrombolysis therapy is recognised as the most effective treatment for acute ischaemic stroke. However, elderly patients over the age of 80 have been underrepresented in many large scale trials investigating tPA therapy and its impact on longer term functional outcomes.

Method: A retrospective study was conducted using data collected from patients admitted into the Austin Stroke Unit who received tPA therapy for acute ischaemic stroke over a three year period. Data analysed included age, sex, stroke risk factors and time to treat. The National Institute of Heath Stroke Scale (NIHSS) was used as a marker of neurological deficit at 24 hours post stroke. Outcomes were measured using the Modified Rankin Scale (mRS) at day 90, where 0-1 was considered a favourable outcome.

Results: 141 patients received thrombolysis during the study period. 79 patients were <80 years and 53 were \(\geq\) 80 years old. A higher NIHSS score, was noted in the \(\geq\) 80 year group, compared to patients <80 years with median scores of 15 \& 10 respectively (\(p=0.006\)). Younger age and lower NIHSS score were both significantly associated with favourable outcomes. Using multivariate logistical regression, including an adjustment for NIHSS \(\geq\) or < 15 on presentation, younger patients were 9 times more likely to have favourable outcomes at day 90 than patients in the \(\geq\) 80 year group (\(p < 0.001\)).

Conclusions: In this retrospective, non-randomised study there was a substantial difference in 3 month functional outcome observed between patients aged \(\geq\) 80 and <80 years following tPA over the three year study period. This may be due solely to the poorer prognosis for elderly patients after significant stroke rather than an effect of tPA. Further randomised clinical trials in this subgroup of patients are indicated to show that the benefits of tPA following stroke are maintained in patients aged \(\geq\) 80.
FAMILIAL NEONATAL EPILEPSY: CLINICAL AND MOLECULAR FEATURES IN 36 FAMILIES

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Objective: Two autosomal dominant epilepsy syndromes may present with neonatal seizures: Benign familial neonatal epilepsy (BFNE) is associated with mutations in potassium channel genes (KCNQ2 and KCNQ3)¹, while mutations in SCN2A have been found in benign familial neonatal-infantile epilepsy (BFNIE)²,³. These conditions are considered to be self-limited, although seizures later in life have been reported in about 15% of BFNE cases⁴. This study delineates the clinical and molecular features of 36 families with familial neonatal epilepsy to better understand the prognosis for these families and consider whether a clinical and molecular overlap exists between BFNE and BFNIE.

Methods: We screened families for KCNQ2, KCNQ3 and SCN2A mutations and reviewed the neonatal seizure course and occurrence of seizures later in life.

Results: Thirty-three families were clinically classified as BFNE. Twenty-six different KCNQ2 mutations and one KCNQ3 mutation were found in 28 BFNE families. Two families had mutations of SCN2A. Seizures after the neonatal and infantile period were seen in 32% of individuals with KCNQ2 mutations. The mutation-negative BFNE families were clinically indistinguishable from the mutation-positive families. Three families had additional features excluding them from the diagnosis of BFNE; molecular lesions have been identified in two, and the other family remains unsolved.

Conclusions: Most of our families with familial neonatal epilepsy fit the clinical syndrome of BFNE. The molecular cause was found in 91% of families. Seizures later in life are more common in BFNE than previously reported and may be associated with a greater number of seizures in the neonatal period.

ALTERED SENSITIVITY OF CARDIOVASCULAR CONTROLLING NEURONS IN THE MEDULLA OF OBESE ANIMALS MAY CONTRIBUTE TO THE DEVELOPMENT OF OBESITY-RELATED HYPERTENSION.


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The rostro ventrolateral medulla (RVLM) contains spontaneously active neurons that play a major role in arterial pressure (AP) regulation. The gut hormone cholecystokinin (CCK) acts via gastrointestinal vagal afferents to facilitate blood flow to the gut following food ingestion. This vasodilator response is achieved via inhibition of a subclass of RVLM neurons. Our aim was to determine whether obesity is associated with altered sensitivity to CCK in these neurons.

Male Sprague-dawley rats (n=32) were placed on either a medium high fat diet (MHFD; n=24) or low fat diet (LFD control animals; n=8) for 15 weeks. Following this period, animals were anaesthetized and artificially ventilated. Animals were placed into a stereotactic frame and electrophysiological techniques were used to identify cardiovascular-controlling RVLM neurons. Presympathetic vasomotor neurons were further studied for responsiveness to CCK (0.05 – 4ug/kg). For analysis MHFD rats were stratified into obesity prone (OP; n=8) or obesity resistant (OR; n=8) post-hoc, depending on whether their weight gain fell into the upper or lower tertile.

OP animals exhibited increased weight gains compared to OR or LFD rats (P<0.001 for both). AP was elevated in OP (117.1±5.6 mmHg) when compared to LFD (95.1±4.4 mmHg; P<0.01) or OR (99.4±2.8; P<0.05) animals. Inhibitory neuronal responses to CCK were observed in OR and control animals but these responses were diminished or completely reversed in OP animals.

These findings suggest that altered CCK sensitivity at the neuronal level may be associated with reduced vasodilator responses that may contribute to elevated arterial pressure in obesity.

FROM CLINICAL PRACTICE TO MOLECULAR MEDICINE AND BACK AGAIN.

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BACKGROUND. Molecular medicine is having a major impact on many clinical areas. In epilepsy, clinical genetic and molecular genetic advances have had significant impacts on diagnosis, counselling for prognosis and recurrence risk, and for directing treatment. AIM. We assessed our experience in molecular diagnosis using a traditional sequencing approach of the two most important epilepsy genes, the sodium channel gene SCN1A and the glucose transporter SLC2A1. This was performed at the interface between research and clinical practice and is a prelude to studies using emerging high throughput massively parallel sequencing technology. METHOD. Patients analysed for SCN1A were selected based on a clinical diagnosis of the syndrome of genetic epilepsy with febrile seizures plus, including its severe form known as Dravet syndrome. SLC2A1 was studied in a broad range of subjects with generalized epilepsies. All coding exons and intron-exon boundaries were sequenced by conventional Sanger sequencing. RESULTS. Causative SLC2A1mutations were found in ~2% of nearly 1000 patients screened. In the subset of cases with early-onset absence epilepsy the frequency of mutations was 10%. For SCN1A, ~100 cases have been studied and 10% of the selected patients were positive for a pathogenic allele. CONCLUSIONS. These findings were clinically valuable and have altered management in positive cases. The cost of conventional sequencing is high ($700-2,000 per subject) so the relatively low rate of positive findings is a challenge for economics of service delivery. The low success rate is contributed to by genetic heterogeneity of epilepsies and the complex genotype-phenotype correlations that exist. Many other rare epilepsy genes are known and additional ones will be discovered. It is currently not feasible to sequence all epilepsy genes in each patient. However, in the near future new massively parallel sequencing approaches will be applied to epilepsy to provide cost-effective and high-throughput genetic diagnosis.
INFLAMMATORY RESPONSE AFTER INJURY IN THE RAT CNS - MACROPHAGES AT THE INJURY SITE EXHIBIT DIFFERENT PHENOTYPES

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Aims. The aims of this study are to (1) verify that different macrophage phenotypes exist after injury to the CNS in the adult rat, and (2) develop immunohistochemical markers of the different macrophage phenotypes. Hypotheses. (1) At least two different macrophage phenotypes exist within the injured CNS - macrophages located at the wound edge support regeneration, while wound core macrophages do not. (2) These phenotypes can be identified using immunohistochemical biomarkers and by their location in the wound. Methods. Adult rats received bilateral brain axonal injury using a Scouten wire-knife, and were sacrificed after two weeks. OX42-positive macrophages located at the wound core or edge were laser-captuolated into Trizol. RNA was prepared and purified with a Qiagen RNeasy kit. cDNA was prepared using the Invitrogen Superscript III Amplification Kit and the gene expression profiles compared on Affymetrix Rat Genome 230 2.0 Array. Results. 30000 genes were analyzed, of which 928 genes had a minimum 2-fold change in expression. Ninety genes exhibited a minimum 30-fold change - between macrophages from the two locations. We identified potentially targetable families of genes and have shortlisted possible immunohistochemical markers that may identify, and differentiate between the supportive and non-supportive macrophages. Conclusion. The macrophages from two different locations at the wound exhibited considerable differential gene expression, even though they were isolated found less than 100 µm apart. Limiting the development of cytotoxic or non-supportive macrophages, or directing macrophage activation towards a growth-supportive phenotype immediately after trauma, may contribute towards creating a cellular environment that encourages repair.

A PILOT TO DETERMINE THE PRACTICALITY OF USING MODIFIED GOLGI-COX STAINING TO ASSESS CORTICAL DENDRITIC MORPHOLOGY AFTER MIDDLE CEREBRAL ARTERY OCCLUSION IN RATS.

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PURPOSE: Whilst experimental stroke studies have showed much promise, a clinically effective acute treatment for stroke other than thrombolysis has yet to be translated into stroke patients. Most assessments of ischemic damage (and potential neuroprotection) have focussed on markers of the cell body with little attention given to damage of neuronal processes. Here we report a pilot using modified Golgi-Cox staining to examine the extent of damage to the dendritic arbour of neurons after stroke in rats. METHODS: Stroke was induced in normotensive WKY and hypertensive SHR rats by thread occlusion of the Middle Cerebral Artery (MCA)(n=19). 24 hours after MCAo the brain was collected and processed for modified Golgi-Cox staining. 150 µm thick coronal sections were cut, and a section 0.2mm anterior of bregma used for staining. With the midline as a reference point, successive neurons spaced 500 µm apart in layers III-V were assessed. RESULTS: Overall, WKY rats had greater dendritic branching than SHR (27±10 vs 18±8, mean±SD). Moving away from the midline, the ability to detect significant branching stopped sooner in the SHR than WKY consistent with prior reports of larger MCA infarcts in this strain. Within the limits of the sampling regime chosen, there were no differences in overall branching pattern between stroke and control hemispheres in either strain (WKY 31:27; SHR 18:18; contralateral:ipsilateral). CONCLUSION: Despite apparent differences at the level of simple visual examination, no differences were detected at microscopy. The confounding effects of significant numbers of cells with microglial morphology and a tendency to “pick” cells with something to measure probably accounts for these discrepancies. An unbiased sampling regime of cells in a volume of tissue is essential.
Background: Growing evidence supports an association between Alzheimer's Disease (AD) and vascular risk factors (VRF) such as hypertension, diabetes, hypercholesterolaemia, obesity and smoking. Studies also suggest that associations may be influenced by timepoint (eg mid-or late-life), Apolipoprotein ε4 (Apoε4) status and gender.

Whereas previously, confirmation of AD required histopathological correlation, imaging with 11C-PiB Positron Emission Tomography (PET) enables quantification of AD-pathology in life. Objectives: To examine whether vascular risk burden is associated with presence of AD-pathology using 11C-PiB PET in cognitively normal elders free from clinical vascular disease, and for interactions with Apoε4 and gender. Methods: 175 participants >60 years with Normal cognition (NC) from the AIBL study, with 11C-PiB-PET, neuropsychological testing, and blood analyses. VRF defined according to guidelines, (Scored as 0-7 for: Hypertension, Diabetes Mellitus/Hyperinsulinaemia, Hypercholesterolaemia, Obesity, Smoking, Chronic Renal Impairment, Hyperhomocysteinaemia); “High VRF burden” defined as >1 VRF. ß-amyloid burden quantified using Standardized Uptake Value Ratio (SUVR) normalized to cerebellum. “High PiB” threshold SUVR of 1.5 as published. Using SPSS Version19.0, chi-square, ANOVA, logistic/linear regression, and General Linear Model were performed with VRF burden, Apoε4 and gender as interaction terms. Results: Adjusting for age, gender and Apoε4, prevalence of High PiB increased with increasing number of VRF (p<0.01), and there was a trend for increasing SUVR with increasing VRF (p<0.05). Age (OR 1.2, 95% Confidence Interval 1.1 -1.2), Apoε4 (OR 9.4, 3.5 -24.9), and VRF score (1.5 1.1-2.3) were independently associated with High PiB Burden. The interaction between VRF and Apoε4 status was also associated with SUVR (p<0.01), but VRF and gender was not (p=0.1). Conclusion: In this sample of cognitively-normal elders, increasing number of VRF was associated AD-pathology and there was a significant interaction with Apoε4 status. Treatment to reduce vascular risk may be protective for both Alzheimer's Disease as well as cerebrovascular disease.

Aim: The fovea is a specialised structure within the light-sensitive retina, which enables high acuity vision at the centre of gaze. The difficulties associated with investigating human foveal development mean that an appropriate model system is required. The purpose of this study was to investigate the development of the fovea in a potential model species, the pigeon (Columba livia). Methodology: To visualise rod cell topography, retinae from pigeons aged from post-hatch day 0 to post-hatch day 42 underwent a whole-mount immunohistochemical process using the rod opsin primary antibody, RET-P1. The density of photoreceptors and ganglion cells were quantified using differential interference contrast and confocal microscopy, respectively. To investigate formation of the foveal pit, eyes from pigeons aged from embryonic day 7 to post-hatch day 28 were sectioned and stained with cresyl violet. Results: The pigeon foveal pit was observable one week after hatching. The density of photoreceptors and ganglion cells increased significantly with age, while ganglion cell density decreased. Conclusion: During development of the pigeon fovea, photoreceptor density increases significantly, while ganglion cell density decreases. The pigeon fovea develops at a relatively late stage and is slow to reach maturity. The pigeon fovea, therefore, has a number of histological and developmental similarities with the human fovea.
THE ROLE OF RECURRENT COPY NUMBER VARIANTS IN GENETIC GENERALISED EPILEPSIES

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Aim – To examine the association between genetic generalised epilepsy and copy number variants. Background - Copy number variants (CNV) are small deleted or duplicated chromosomal regions. CNV are associated with developmental disability, particularly intellectual disability and autism. Recurrent CNV are also associated with genetic (idiopathic) generalised epilepsy (GGE); despite intellectual disability excluding this diagnosis. A deletion at 15q13.3 has been confirmed in GGE while deletions at 15q11.2 and 16p13.11 have recently been reported. Methods – we studied 365 GGE probands and 65 with epilepsy suggesting GGE but autism or intellectual disability that would exclude the diagnosis (DD-GGE). Recurrent CNV were screened by loss of heterozygosity and confirmed by comparative genomic hybridisation (CGH). All DD-GGE probands had CGH. 400 blood bank and published controls were used.

Results – 15q11.2 microdeletion was seen in 5/365 GGE probands (1.1%, controls 0.2%, p=0.003, OR=5); 16p13.3 microdeletion in 3/365 GGE probands (0.8%, controls 0.07%, p=0.007, OR=14). One DD-GGE carried each microdeletion (1.5%). DD-GGE showed a higher rate of the established 15q13.3 microdeletion (4/65, 6%) than either GGE (1%, p<0.05) or ID (0.3%, p<0.05). 16/65 (25%) DD-GGE probands carried a likely pathogenic CNV. Conclusions – We confirmed the association of the 15q11.2 and 16p13.3 with GGE. The “dual disability” phenotype shows a very high rate of CNV. For the 15q13.3 deletion this is significantly higher than ID or GGE alone and the total rate of CNV is strikingly higher than that seen in ID (25% vs. 10%). CNV contribute strongly to epilepsy and particularly to the intersection of epilepsy and intellectual disability.
The Diabetes Educators (DE) from two metropolitan hospitals were inspired by an abstract by Corbin, A. et al. (1) that led to a similar study being conducted.

Aim: To determine if diabetes self-care information was recalled by hospital patients following discharge.

Methods: The pilot study inclusion was directed at previous inpatients taking insulin. Documentation was reviewed, a questionnaire developed and a telephone survey conducted.

Results: The questionnaire comprised 30 questions. Of the 129 inpatients seen during a two month period in 2011, discharge documentation was summarised on 38 patients who commenced or changed insulin. Using this information, the DE telephoned twenty nine patients within 28-30 days post discharge. Of these, 48% Caucasian mean age 55 years, 83% secondary or tertiary educated, 67% male and 90% commenced insulin for the first time. The significant findings are shown in the table below.

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<tr>
<th>Questionnaire</th>
<th>Discharge Documentation</th>
<th>Patient Recall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q12. Do you record your blood glucose results?</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Q1. Whilst in hospital, were you told you had high blood sugars?</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Q22. Did you receive a diabetes information kit?</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Q7. What time do you take your insulin?</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Q10. Have you received your new or upgraded NDSS card?</td>
<td>93%</td>
<td>83%</td>
</tr>
<tr>
<td>Q23. Follow up with health professional</td>
<td>86%</td>
<td>79%</td>
</tr>
<tr>
<td>Q5. What is the name of your insulin?</td>
<td>100%</td>
<td>76%</td>
</tr>
<tr>
<td>Q11. Did you obtain a sharps box?</td>
<td>86%</td>
<td>69%</td>
</tr>
<tr>
<td>Q21. Did you receive any nutrition advice from the dietitian?</td>
<td>72%</td>
<td>48%</td>
</tr>
<tr>
<td>Q17. How do you treat a hypo?</td>
<td>100%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Diabetes self care was recalled by patients with differences noted between discharge documentation and patient recall. The greatest discrepancies were in the area of nutrition and hypoglycaemia management.

Conclusion: This study has been useful and highlighted areas of concern. The outcomes require further research into strategies which may improve information delivery, documentation and retention.

PSYCHOMETRIC EVALUATION OF THE PATIENT-CENTRED ACUTE CARE OF OLDER PEOPLE (PACO) QUESTIONNAIRE.

D. Edvardsson¹, D. Fetherstonhaugh¹, S. Crowe²

¹La Trobe University, Bundoora, VIC, Australia
²Nursing Services, Austin Health, Heidelberg, VIC, Australia

The aim of this study was to evaluate psychometric properties of a self-report assessment scale measuring the extent to which patient-centred care of older people with cognitive impairments is provided in acute hospital wards. Older people with cognitive impairment are frequently admitted to acute hospitals, and their needs are not always met through standard care practice. A cross-sectional design was employed to distribute the Patient-centred Acute Care of Older people (PACO) assessment scale to a sample of Austin Health nursing staff (n=212). Psychometric evaluation was performed using statistical estimates of validity and reliability. The results show that the final 15-item questionnaire consists of three subscales, ‘using cognitive assessments and care interventions’, ‘using evidence and cognitive expertise’, and ‘individualising care’. Content and construct validity was satisfactory as estimated through Delphi assessment, factor and item analysis. Reliability estimates were highly satisfactory as evidenced through item-total correlations between 0.40 and 0.67, and a total Cronbach's alpha of 0.87, with subscale Cronbach's alpha values of 0.74, 0.79 and 0.78 respectively. The PACO scale makes a valuable contribution to the literature by being the first valid and reliable scale to measure the extent to which staff report that their care practices enable valid detection of cognitive impairment in older patients, and employ interventions to meet the needs associated with cognitive impairment. The scale enables descriptions and comparisons between wards, correlating care practices and patient outcomes, and/or evaluating the impact of interventions.

THE PREVALENCE OF PATIENT-CENTRED OUTCOMES AT THE AUSTIN HOSPITAL – A CROSS-SECTIONAL STUDY.

D. Edvardsson¹, D. Fetherstonhaugh¹, S. Crowe²

¹La Trobe University, Bundoora, VIC, Australia
²Nursing Services, Austin Health, Heidelberg, VIC, Australia

The aim of this study was to evaluate the extent to which nursing staff report patient-centred outcomes at the Austin Hospital. Patient-centred care, commonly described as care that caters for the emotional and psychosocial needs of patients, is increasingly being advocated as a key hospital quality indicator in Australia and overseas. A cross-sectional design was employed to distribute the Person-centred Climate Questionnaire (PCQ) to a sample of Austin health nursing staff (n=212). Data were subjected to descriptive statistics and t-tests. The results show that the respondents were generally satisfied with the extent to which care provided was patient-centred. Analyses show that the majority of staff agreed that the patients were in safe hands at the wards (98%) and that it was easy for inpatients to: receive visitors (93%); have someone to talk to (91%); and keep in touch with family members (87%). However, the physical environment was not perceived to be as person-centred; with 72% of staff responding that the wards were not peaceful, 49% reporting a lack of positive distractions in the environments, and 40% indicating a lack of aesthetics features in the environment. Conclusively, the findings indicate that Austin Hospital staff generally perceive the care provided as being patient-centred, even if the physical environment could be enhanced. As the Australian Commission on Safety and Quality in Health Care recently have recommended patient-centred care as a key quality indicator, this study provides an important baseline measure and insight into areas for improvement.
CONSIDERING THE ORAL HYGIENE AND CARE OF HOSPITALISED ACUTE MEDICAL AND MENTAL HEALTH PATIENTS


1Nursing, Austin Health, Heidelberg, VIC, Australia
2ACU, Melbourne, VIC, Australia

Aim: This study is a two phased project to determine the best available evidence in relation to best practice of the oral hygiene of hospitalised acute medical and mental health patients. Objectives: Phase one - To describe existing screening and referral practices for patient's oral hygiene needs as baseline project data. Phase two - To improve screening, intervention and/or referral to appropriate oral care, and To develop and test a clinically relevant multidisciplinary care pathway that will meet the needs of individuals with oral hygiene needs. Methods: A collaborative mixed methods study. Results: These results are a presentation of phase one. A retrospective audit of 150 randomly selected medical records for a 4 week period between December 1st 2009 and December 1st 2010 was undertaken to provide baseline data on current screening and referral practices for documented oral hygiene needs of hospitalised patients. Cases eligible for inclusion in the study were adult patients admitted to 2 acute general care wards and 2 mental health wards in the hospital. Inter-rater reliability was 85%. Conclusions: There is little available data on current screening practices resulting in limited understanding of the most appropriate time to intervene in order to improve oral health outcomes. Oral hygiene practices were inconsistent across the wards involved in this phase of the project. In the next phase, this collaborative mixed methods project will examine the effectiveness of a clinical pathway to identify the oral hygiene needs of hospitalised patients.

STAFF ATTITUDES AND CARE PRACTICES RELATING TO OLDER PEOPLE WITH COGNITIVE IMPAIRMENT IN THE ACUTE CARE SETTING.

L. MacDonald, D. Edvardsson

1La Trobe University/Austin Health Clinical School of Nursing, Heidelberg, Australia
26 West, Austin Health, Heidelberg, VIC, Australia

Aim: Older people with cognitive impairment are major hospital care consumers and despite this, their care needs are not always catered for. The aim of this study was to: explore staff attitudes toward older people with cognitive impairment; and the association between attitudes and current ward practice. Method: A cross-sectional design was employed to distribute the Patient-Centred Acute Care of Older People assessment scale together with a component assessing staff attitudes toward older people, to a sample of Austin Health nursing staff (58% response rate; n=212). Results: Descriptive statistics reveal the proportion of nursing staff agreeing, for example that: older patients with cognitive impairments are not suitable for an acute care setting (38%); staff have more important things to do than managing confused older patients (52%); caring for older people with cognitive impairments takes too much time (47%); and cognitive impairments are only problematic if expressed as adverse behaviours/events (63%). The results further display that staff with positive attitudes rated their wards as having significantly (p<0.05) more care practices that enable valid detection of cognitive impairment and care interventions that meet the needs associated with cognitive impairment, than staff with negative attitudes. Conclusion: These findings indicate that a surprisingly large proportion of staff held negative views of older people with cognitive impairment, even though this population is highly prevalent in the acute care setting. The findings also highlight the association between attitudes and care provision, and suggest that in working towards practice change, staff attitudes are central.
NURSING DOCUMENTATION: DEVELOPMENT OF AN ASSESSMENT TOOL TO IMPROVE PRACTICE

M. Gwynne, T. Griffiths  
Day Oncology, Austin Health, Heidelberg, VIC, Australia

Background: Documentation is an important instrument that nurses use to illuminate assessment and intervention outcomes to colleagues. Assessment and care planning tools facilitate standardized documentation and contribute to optimizing patient care.

A clinical audit was conducted of current nursing documentation and patient assessment pre treatment in Day Oncology. This identified significant gaps highlighting the need for improvement leading to a project to develop and implement a revised tool for pre treatment assessment and care planning.

Aims: To develop a new nursing documentation tool that optimizes patient assessment and care planning for patients undergoing cancer treatment.

Method: A literature review was conducted and current practices from external sources were explored. Input was sought from nursing and medical staff within Day Oncology. A new form was devised and trialed for a period of one week followed by an evaluation by nursing and medical staff.

A repeat clinical audit of 50 forms was undertaken in order to highlight changes in practice.

Result: Evaluation of the new nursing form revealed a high level of satisfaction regarding ease of use, improved communication with respect to nursing interventions and increased confidence in patient assessment skills.

In addition, audit results showed improved documentation of nursing interventions, improved adherence of medico legal requirements such as date, time and relevant signatures, and comprehensive discharge planning for patients.

Conclusion: The revised pre treatment assessment and care planning tool has enhanced nursing documentation and communication regarding patient care amongst the treating team leading to improved quality care delivery in Day Oncology.

INCIDENCE AND PREVENTION OF INADVERTENT PERIOPERATIVE HYPOThERMIA

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Post Anaesthesia Recovery Unit, Austin Health, Heidelberg, VIC, Australia

AIM: Perioperative hypothermia remains a common occurrence for patients undergoing anaesthesia, despite the development and dissemination of clinical practice guidelines for the prevention of unplanned perioperative hypothermia. This study was aimed at establishing the incidence of perioperative hypothermia within the operating suite and assessing the efficacy of prewarming in the prevention of inadvertent perioperative hypothermia.

METHOD: The study was conducted in two phases using a standardised data collection tool which noted demographic data, length of surgery, type of anaesthesia, and warming methods utilised. Baseline data was collected prior to the introduction of prewarming for hypothermic patients and secondary data was collected 12 months post implementation of prewarming for hypothermic patients.

RESULTS: Baseline data collection included 78 patients with a mean preoperative temperature of 36.2°C. 35.8% (n = 28) were classified as hypothermic with a core temperature of less than 36°C preoperatively. Intraoperative warming methods were used on 94.7% (n = 74) of patients surveyed. The distribution of patient temperatures on arrival in PARU displayed a drop in the average temperature to 35.8°C, with 48.6% (n = 38) of patients hypothermic on arrival to PARU. Secondary data collection included 60 patients with a mean preoperative temperature of 36.03°C. 46% of these patients were classified as hypothermic during the preoperative period. Of these patients, 23.3% had a forced air warmer applied preoperatively. Intraoperative warming methods were used on 93.33% of patients surveyed. On arrival in PARU patient temperatures displayed a decrease in average temperature to 36.0°C.Compared to the 46% of patients that were hypothermic preoperatively 30% of patients presented to PARU hypothermic. Baseline results show an average drop in temperature pre to post operatively of 0.4°C, secondary data, post implementation of prewarming, show an average drop in pre and post operative temperature of 0.03°C.

CONCLUSION: Data examined supported the efficacy of preoperative warming in the prevention of inadvertent perioperative hypothermia.
INTRODUCTION OF THE HEALTH ASSISTANT NURSING ROLE AT AUSTIN HEALTH
S. Crowe, G. Knuckey, K. Owen
Nursing Services, Austin Health, Heidelberg, VIC, Australia

This poster will give an overview of the model and the evaluation undertaken by a busy tertiary-level Victorian health service relating to the implementation of a new role into the ward team to assist nurses, called the Health Assistant Nursing.

In 2008 the health service conducted a feasibility study focusing on the introduction of a Health Assistant Nursing role. Major findings from the feasibility study were that there is widespread acknowledgement of the changing health workforce and the need for a new direction for nursing. Nurses were willing to look at another role with the implementation of a satisfactory governance structure. Following funding support, in July 2009 the health service undertook a pilot program introducing a brand new Health Assistant Nursing role into three acute care wards. As this role was completely new to Victoria, the model was established having regard for publications and site visits that gave insight to lessons learnt from the introduction of similar roles both within Australia and overseas.

Throughout the pilot the value of this new role was analysed utilising a mixed method approach, which included feedback from both staff and patients utilising focus groups and questionnaires, together with analysis of patient outcome data and economic impact data.

What was clear is that the implementation of the Health Assistant Nursing role and the model used has been an overwhelming success. The reasons for this success are multifaceted and will also be summarised in the poster. Key achievements attributed to this new role are:

- Strong support from nursing staff, with increased staff morale.
- Improved levels and quality of patient care – particularly relating to personal hygiene, grooming, nutritional intake, ward environment and patient movement.
- Increased patient satisfaction.
- Clear establishment and understanding of the scope of practice of the new role, and successful integration into the ward team.

CD-BASED AND INSTRUCTOR-LED BASIC LIFE SUPPORT SKILLS TRAINING: A COMPARISON
K. Mardegan1, M. Schofield2, G. Murphy2
1MEU, Austin Health, Heidelberg, VIC, Australia
2Public Health, LaTrobe University, Bundoora, VIC, Australia

Basic Life Support (BLS) is a life saving skill. However, there are reported limitations in the BLS skills of both health-care professional and lay people. Traditional instructor-led training approaches are also resource and time intensive. This exploratory study evaluated the effectiveness of a CD-based BLS skills training program that included unsupervised manikin practice with a Traditional instructor-led BLS skills training program involving demonstration and supervised practice.

METHOD: The study used a quasi-experimental post-test design. The sample consisted of two cohorts: Novice second-year undergraduate Nursing students (n=187) and Practising Nurses (n=107) in their first year of hospital employment. Participants were allocated in blocks to the two intervention groups based on natural groupings. BLS skills were assessed at 1 week post training.

RESULTS: No statistically significant differences were found between the CD and Instructor-led BLS training methods in the BLS skills of Novice and Practising Nurses at 1 week post training. There was also a low level of competence post-training across both groups.

CONCLUSION: A CD-based BLS skills training program, which included unsupervised manikin practice has been shown to be comparable to a resource intensive Traditional instructor-led BLS skills training program, however, competence is less than optimal and implies the need for ongoing efforts to develop and evaluate BLS skills training programs which can achieve high rates of competence.
WHAT CALCULATIONS DID OUR INSULIN PUMP PATIENTS START OUT ON?  
L. Roberts, V. Stevenson  
Diabetes Education, Austin Health, Heidelberg, VIC, Australia  

Background: The Diabetes Educators (DE) at a metropolitan hospital were interested in reviewing the continuous subcutaneous insulin infusion (CSII) start rates of patients using standard existing protocols.  

Aim: To profile patients start up pump calculations.  

Method: Data was analysed mainly from post pump initiation clinic letters sent to the referring endocrinologist from the DE.  

Results: Data was compiled between July 2008 - April 2010 for 27 type 1 patients commencing CSII for the first time, CSII upgrades were excluded. All 27 commenced on one background basal rate, all used the same brand meter, had advice for BGL testing, management of hypoglycaemia, hyperglycaemia and had 24 hour telephone contact. The characteristics and CSII commencement rates of these patients are shown in the tables below.  

Table 1. Paediatric CSII data  

<table>
<thead>
<tr>
<th>Total 11 100%</th>
<th>*Age (yrs)</th>
<th>*Yrs of DM</th>
<th>*Ht (cm)</th>
<th>*Wt (kg)</th>
<th>*Basal (units/hr)</th>
<th>*Bolus (I:CHO g)</th>
<th>*ISF (1unit:mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (n=7)</td>
<td>10±3.76</td>
<td>2.2(0.4-6)</td>
<td>146</td>
<td>39</td>
<td>0.56(0.35-0.85)</td>
<td>1:20.3(13-29)</td>
<td>1:4(2.5-5.4)</td>
</tr>
<tr>
<td>M(n=4)</td>
<td>11±4.90</td>
<td>7(2-10)</td>
<td>150</td>
<td>45</td>
<td>0.83(0.2-1.3)</td>
<td>1:22.3(8-58)</td>
<td>1:4.8(1.2-13)</td>
</tr>
</tbody>
</table>

Eleven children were of similar age, height, weight, had similar mean bolus ratios, females commenced CSII earlier with lower basal rates. Sixteen adults were of similar age, mostly overweight, females commenced CSII earlier with a slightly higher basal rate. Interestingly, paediatric males had similar mean basal rates to adult males. Paediatric females had approximately 50% less basal rates of adult females. Compared to adults, children required approximately half of the bolus ratios.  

Conclusion: This information provided a useful profile of how beginner CSII patients started out. The reasons why children commence pumps earlier than adults needs further exploration.  

DIABETES AT MENTAL HEALTH  
E. H. Cornish  
Diabetes Education, Austin Health Repat site, Heidelberg, VIC, Australia  

Introduction/Background A diabetes service has been initiated within an outpatient mental health service at Austin Health. People with a mental illness have many additional risk factors for the development of type 2 diabetes but are unlikely to access the Diabetes Complications and Assessment Service (DCAS) Methods A Credentialed Diabetes Educator (CDE) who is also a psychiatric nurse will attend the mental health clinic for 6 hours weekly, commencing January 2011. She will initiate a database of all patients and respond to abnormal results in consultation with the patient, and treating team. Collaboration will improve the ability of mental health staff to manage diabetes. It is hoped that the CDE can form an initial rapport with the patient by commencing diabetes education at the mental health clinic and arrange annual DCAS review, ensuring the patient sees an endocrinologist, podiatrist and dietician. The clinic is bulk billed and the same CDE works across both mental health and DCAS sites, ensuring continuity for the client. Quality of care is enhanced by the electronic patient record system which is accessible both teams from any location.  

Results The service has only been running for 8 weeks so results are limited. Data shows the mental health clinic has 260 clients of whom approximately 50% completed diabetes screening in the past 6 months. Steps have been taken to improve pathology testing in the inpatient unit, Clozapine Clinic . Conclusion Review of medical histories of clients with known diabetes has show poor attendance for endocrine review appointments. These clients have been offered initial follow up at Diabetes at Mental Health. Some clients with diabetes are being well managed through shared care with their GP. It is hoped that this flexible, collaborative approach will result in improved diabetes management for people with a mental illness.
THE ENDOSCOPY PATIENT EXPERIENCE
L. Bujas
Surgery and Endoscopy Centre, Austin Health, Heidelberg, VIC, Australia

Aim: To identify ways in which the patient experience of endoscopy services at Austin Health could be improved.

Method: Twenty-two patients who had undergone an endoscopy in 5 days in February 2011, were randomly selected for interview the day following their endoscopy. 3 nurses conducted semi-structured telephone interviews with the selected patients. After being asked routine post-procedure follow-up questions, patients were asked for feedback regarding their experience of the service (for the period from making the booking to the day following their procedure) and were asked how the service could be improved.

Results: All 22 patients telephoned agreed to participate in the interviews. While responses were overwhelmingly positive, there were ten issues of concern identified by patients. ‘Long waiting times on the day of the procedure’ and ‘uncomfortable and slippery trolleys’ were reported by 23% (5 patients) each. A further 18% (4 patients) patients reported ‘excessive waiting time between booking for a procedure, and the procedure

Conclusions: The patient experience can be significantly improved through strategies to reduce patient waiting times for endoscopy and the time on the trolley on the day of the procedure, and reducing the time between endoscopy booking and the procedure.

NURSES' ATTITUDES TO WORKING WITH OLDER PEOPLE IN ACUTE CARE
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²Melbourne Graduate School of Education, University of Melbourne, Parkville, VIC, Australia

Introduction: There is little evidence that factors influencing attitudes to older persons have been investigated (Moyle 2003). Changes to service delivery models within acute health have meant that there has been an increase in Day of Surgery Admissions (DOSA) and a decrease in length of stay. Many younger patients are cared for in the community supported with funded programs. Therefore, in-patient populations in acute care are generally older, with greater acuity and increasing co-morbidities. Australia expects an increase from 4.3 million older persons in 2021 to around 6.8 million in 2051 (Australian Bureau of Statistics (ABS, 2008).

Aim: The aim of this study is to build on existing research (Courtney, Tong and Walsh 2000; McLafferty 2005; Wray and McCall 2007; Poole 2009), with a particular focus on immersion in practice and the impact of experience on nurses' attitudes to working with older people.

Methods: This study is ethnographic and utilized individual semi-structured interviews with 15 nurses. The interviews were transcribed verbatim and thematically analysed.

Results: Three themes emerged from the analysis : Role-modelling ; Dependence and Relationality.

Conclusions: Immersion in clinical practice and socially constructed reflection impact nurses' attitudes to working with older people in acute care.

The themes have informed the design of a professional development program : Achieving Relational Reflection
HOW TO GROW A CARDIAC NURSE AND WATCH THEM BLOOM INTO CRITICAL CARE TRAINED NURSES

K. M. Lumsden
CNED, Austin Health, Heidelberg, VIC, Australia

Background: Austin Health has run a PAP (Practice Advancement Program) for nurses completing their Graduate Nurse Year (GNY) program for 6 Years. Many of these nurses came to the Cardiac & Thoracic Unit and having gained a large amount of experience and knowledge often then left to do other courses.

Methods: Following a consultation process with the stakeholders including Nurse Unit Managers, Educators, Senior nurses and management a program was developed. The program involved employing a variable number of what would be called "Cardiac PAPs" for 12 months rotating within the cardiac areas of the hospital. Six nurses completed the first program, which involved rotations to cardiac catheterisation laboratory, coronary care and the cardiothoracic ward.

The aims of the program were:
To provide an introductory level of knowledge to PAP students.
To retain PAP students in the cardiac areas of the hospital.
To achieve at least a 50% rate of cardiac PAP's advancing to the Cardiac Course.

Results: Since 2004, 20 nurses have undertaken general (non cardiac PAP) in the Cardiac & Thoracic Unit and 16 nurses have completed the cardiac PAP (commencing in 2008). In the three years that both programs have run 69% of nurses returning to cardiac areas post the GNY have completed Cardiac PAP.

Discussion: The Cardiac PAP has allowed us to recruit staff and maintain them in the cardiac units of the hospital. Programs similar to this have been adopted at Austin Health in Mental Health, Operating Suite and Rehabilitation.

AN EXPLORATION OF GRADUATE NURSES' PERCEPTIONS OF THEIR PREPAREDNESS FOR PRACTICE AFTER UNDERTAKING THE FINAL YEAR OF THEIR BACHELOR OF NURSING DEGREE IN A UNIVERSITY-BASED CLINICAL SCHOOL OF NURSING.

L. E. Pascoe, E. A. Watt
La Trobe University/Austin Health Clinical School of Nursing, La Trobe University, Heidelberg, VIC, Australia

The nursing literature continues to give ongoing attention to university educated nurses preparedness for practice in the first year following graduation. This study explored the impact of a university-based clinical school of nursing experience on graduate nurses' perceptions of their preparedness for practice. This paper reports on a descriptive explorative study of ten registered nurses undertaking their graduate year program in the same hospital where they attended the university-based clinical school of nursing. Data were gathered through in-depth individual interviews which were audio-recorded, transcribed verbatim, and analysed to reveal themes and sub-themes. Thematic data analysis revealed three key themes: 'the university away from the university', 'being situated in a clinical school within a hospital' and, 'engagement with practice'. The outcome of the experience of being situated in a university-based clinical school of nursing contributed to the participants' sense of being prepared for practice as a graduate nurse.
NURSE Rounding: The Introduction and Implementation of Increased Patient Surveillance

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²School of Nursing & Midwifery, LaTrobe University, Bundoora, VIC, Australia
³ACU, Melbourne, VIC, Australia

Aim: The aim of this study is to introduce and implement Nurse Rounding to increase patient surveillance as a means of managing risk of patient falls, pressure injuries and Code Blue/MET calls.

Methodology: This is a two phased mixed methods study that will be conducted across Austin Health.

Phase one: It is anticipated that nurses engaged in the Nurse Rounding project will round on their patients hourly based on an adapted version of Woodard's ‘4P’s’ (2009) (pain, panning/toileting, position, and proximity). Nurses will document their rounds on a nurse rounding tool. Baseline data will be obtained four weeks before Nurse Rounding education is provided to nurses on the two participating wards, an acute medical and an orthopaedic ward. At four weeks and at six months after the implementation of Nurse Rounding on the two wards data will be obtained related to falls, pressure injuries, Code Blue/Met calls and Nurse Call bells. Education will be delivered in double staffing times for day/evening staff and at start/end handover for night staff. An education pack will be given to staff which contains of an information sheet, FAQ sheet and a copy of the tool. Nurses engaged in Nurse Rounding will also be invited to attend focus groups to obtain their feedback on Nurse rounding.

Phase two: Following successful completion of phase one Nurse Rounding will be introduced across the hospital. Key outcomes measures are falls, pressure injuries, Code/Blue MET calls and nurse calls.

Conclusions: It is anticipated that Nurse Rounding will increase patient surveillance and patient satisfaction with a reduction of patient falls, pressure injuries, and a decrease in nurse calls, with an expected reduction in Code Blue and a rise in MET calls. It is expected that a decrease in call bells will free up nursing time.


Wellness & Supportive Care: Integrating a Holistic Program into the Routine Clinical Care of Cancer Patients in an Ambulatory Setting

T. Griffiths, C. Scott

Day Oncology /cancer Services, Austin Health, Heidelberg, VIC, Australia

Background: Day Oncology is an ambulatory treatment centre at Austin Health which will be integral to cancer services in the proposed new Olivia Newton-John Cancer and Wellness Centre. Wellness is a new concept to nursing and its focus is a shift from only clinical care to one that embraces the concept of holistic care.

The Wellness & Supportive Care Program at Austin Health supports a number of initiatives for patients offered outside of the Day Oncology setting.

Aim: To integrate holistic wellness concepts into routine cancer care for patients within Day Oncology.

Method: A range of pilot programs were introduced in the ambulatory centre which included education of nurses in supportive care screening and identification of patient needs; the introduction of a supportive care screening tool including referral pathways; introduction of massage and introduction of art therapy for patients and their carers.

Result: Nurses reported increased skills and understanding in supportive care screening and referral process, with most patients now being routinely screened at commencement of treatment. Art therapy has commenced through the clinical placement of a Master's student. Plans are underway for the introduction of massage for cancer patients. Uptake of the programs by patients has been positive.

Conclusions: With the appropriate education, training and support of health professionals, a range of wellness & supportive care programs can be successfully integrated into routine care for cancer patients in Day Oncology.
THE POINT PREVALENCE STUDY TO ASSESS THE ACUITY PROFILE OF A SURGICAL WARD

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2Anaesthesia, Austin Health, HEIDELBERG, VIC, Australia

Introduction: Studies have found that hospital patients are increasingly more complex. For the surgical patient, this predisposes them to postoperative complications that are medical in nature. A recent review of a surgical ward recommended the acuity profile of their patients be determined.

Aim: We sought to identify the patient profile of ward 8 West and compare it to the profile of two other wards: a medical (7 West) and another surgical ward (8 North).

Methods: A point prevalence audit was conducted on two surgical and a medical ward in Austin Health on the 9th of May 2011. Various demographic and clinical data were collected on each patient including their co-morbidity status according to set criteria.

Results: A total of 96 patients were audited: 31 (34%) 8 West, 28 (31%) 8 North and 32 (35%) 7 West patients. The median age was calculated for each ward: 8 West = 58.0 years, 8 North = 62.0 years and 7 West = 82.5 years. Co-morbidity loading for each ward was stratified according to the number of criteria each patient met.

- 0 co-morbidities; 8 West = 9.7%, 8 North 25.0%, 7 West = 6.3%;
- 1 co-morbidity; 8 West = 16.1%, 8 North = 39.3%, 7 West = 15.6%;
- 2 co-morbidities; 8 West = 29.0%, 8 North = 17.9%, 7 West = 31.3%;
- > 3 co-morbidities; 8 West = 45.2%, 8 North = 17.9%, 7 West = 46.9%

In addition, the number of medication charts per patient and the median length of stay on 8 West were more reflective of 7 West.

Conclusions: The data suggests that the 8 West patient profile is comparable to a medical ward patient profile, despite a younger median age and with the added complexities that come with caring for the surgical patient.

PRACTICALITIES OF MENU-BASED CHANGES TO IMPROVE DAIRY CALCIUM INTAKE IN AMBULATORY AGED CARE RESIDENTS

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2Dietetics, Monash University, Clayton, VIC, Australia

Low dietary calcium intakes (<600mg/day) are common in low-level aged care residents and contribute to fracture risk. Limited data is available describing menu-based changes to improve dietary calcium intake and none have been comprehensively evaluated. We aimed to increase dietary calcium intake in residents to recommended levels (1300mg/day) via the food service by including 2 additional serves of dairy foods per day to the menu. Dietary intake was assessed using 3-day food intake records in 64 low-level aged care residents (mean age 89 years, 75% females) from two facilities over 6 days throughout 4-week menu cycles before, and after menu-modifications were commenced (12 days total). In consultation with food service staff, menu changes were made, consisting of recipe modifications, adding dairy foods to existing meals, substituting items for dairy foods or using dairy-based accompaniments to meals. Existing food ordering methods were used. Mean baseline dietary calcium intake was 550±187mg/day. During the supplementation period, mean calcium intake increased to 646±290mg/day (p<0.01) During the intervention period calcium intake improved over time, with a higher intake observed in the 4th week relative to the first week (860±386mg/day v 627±344mg/day, p<0.01). Improvements in dairy calcium intake can be achieved through menu modifications however the aim of 2 additional serves of dairy was not obtained. Barriers included time constraints and reluctance to alter menus by food service staff. A more intensive intervention involving additional food service support is required and will be initiated to achieve the desired outcome of dietary calcium intakes at recommended levels.
BIOMARKER DISCOVERY IN THE CERVICOVAGINAL FLUID FOR PRETERM BIRTH USING 2D-DIGE AND MASS SPECTROMETRY

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Preterm birth is defined as delivery <37 weeks' gestation and affects approximately 8-13% of all deliveries worldwide. It is a significant contributor to infant mortality and long-term morbidity, including increased risk of severe impaired neurodevelopment and respiratory complications. The fetal fibronectin (FFN) test is currently the gold-standard test routinely used as a predictor of preterm birth. However, due to its low sensitivity (50%) and poor positive predictive value (9.1%), the application of the FFN test is limited as a negative predictor (97.6%) within 7 days of preterm birth [1]. The aim of this study was to investigate the global changes within the CVF proteome of women with preterm labour and to identify potential biomarkers that may improve the accuracy of predicting preterm birth. A single cervicovaginal fluid (CVF) swab was collected from women presenting to the Emergency Department with symptoms of preterm labour. These women were stratified into two groups: 'true' threatened preterm labour (n=4), who subsequently delivered preterm; and the gestation-matched controls, who delivered at term (n=8). Two-dimensional difference in gel electrophoresis (2D-DIGE) was employed to identify candidate CVF biomarkers of preterm labour. Proteins of interest were subjected to mass spectrometry (nanoLC-ESI-MS/MS) for identification and subsequently validated using western blot analysis. A total of 14 unique differentially expressed proteins were found. The biological roles of the identified proteins are as follows: metabolism (fatty acid binding protein 5, ↓2.1 fold; transaldolase, ↓2.9 fold, vitamin D binding protein, ↑7.9 fold), oxidative balance (thioredoxin-1, ↓2.9 fold; peroxiredoxin-2, ↑2.2 fold), immune response (calgranulin B, ↑3.1 fold; interleukin-1 receptor antagonist, ↓1.7 fold) and protease inhibition (serpin B1, ↓1.9 fold; serpin B6, ↓1.7 fold). These results demonstrate differences in the CVF profile between symptomatic women who deliver preterm to those who ultimately deliver at term.

(1) Riboni F et al. Arch Gynecol Obstet, 2011 Jan 28

MATRIX METALLOPROTEINASE-14 CLEAVES ENDOGLIN TO PRODUCE SOLUBLE ENDOGLIN: A NEW THERAPEUTIC TARGET IN THE TREATMENT OF SEVERE PRE-ECLAMPSIA AND HELLP SYNDROME.

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Aim: To determine whether MMP-14 and Endoglin interact in the pre-eclamptic placenta to produce Soluble Endoglin (sEng). sEng is an anti-angiogenic factor released from the placenta in severe pre-eclampsia. While the mechanism of action of sEng is becoming increasingly understood, its production has remained a mystery. Recently, matrix metalloproteinase-14 (MMP-14) was shown to cleave Endoglin (Eng), producing sEng, in colorectal cancer\textsuperscript{1}. If MMP-14 indeed cleaves Endoglin in the placenta, this interaction provides a specific target for therapeutic development to prevent sEng release.

Method: Human placental samples from normal and severe pre-eclamptic women were analysed via western analysis, immunohistochemistry and proximity ligation assay (PLA) for MMP-14 and Eng expression and interaction. A syncytiotrophoblast cell line was used for \textit{in vitro} assessment of MMP-14 inhibition or siRNA knockdown on sEng levels. A mouse model was used for assessment of MMP-14 inhibition on sEng release \textit{in vivo}.

Results: Both MMP-14 and Eng are increased in pre-eclamptic placenta (p≤0.05), with expression predominately occurring within the syncytiotrophoblast layer. PLA confirmed protein: protein interaction between endogenous MMP-14 and Eng within the syncytiotrophoblast. Treatment of trophoblast cells \textit{in vitro} with both a broad-spectrum MMP inhibitor (GM6001) and MMP-14 siRNA resulted in a significant reduction in the production of sEng (p≤0.05). Furthermore, treatment of a mouse model with the MMP inhibitor GM6001 led to a significant reduction in circulating sEng (p≤0.05).

Conclusions: We have confirmed that MMP-14 is required for the production of sEng within the placenta.

MEASURING HYPOXIA-INDUCED MRNA IN MATERNAL BLOOD TO DETECT FETAL HYPOXIA IN-UTERO

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Aim: To develop a maternal blood test to detect fetal hypoxia in-utero

Background: Inadequate placental transfer of oxygen to the developing fetus leads to fetal growth restriction (FGR). As the fetus becomes increasingly hypoxic, it is at risk of dying. An accurate test to determine the degree of fetal hypoxia and guide timing of delivery does not exist. RNA of feto-placental origin is detectable in maternal blood. It may be possible to profile changes in feto-placental gene expression in response to hypoxia, using feto-placental RNA in maternal blood. Methods: Serial samples of maternal blood were collected from pregnancies complicated by severe FGR (n=20) and compared to healthy matched controls (n=30). Whole genome microarray and PCR-array was performed to identify a candidate hypoxia gene signature for FGR. The proposed hypoxia gene signature (HIF1α, HIF2α, ADM, LDHA) was quantified using RT-PCR. Results: Gene ontology analysis revealed an over-representation of hypoxic pathways in FGR. This was validated using PCR array. The hypoxia gene signature in maternal blood was increased in pregnancies complicated by FGR. There were further incremental increases in the hypoxia gene signature with deteriorating ultrasound estimates of fetal hypoxia. Importantly, there was a significant correlation between the fetal pH at delivery and the hypoxia gene signature. Conclusion: The hypoxia gene signature in maternal blood increased in FGR, reflected progressive fetal hypoxia and correlated closely with the fetal pH at delivery. We have developed a maternal blood test that could be used to determine degree of fetal hypoxia in-utero in severe FGR.

WEB-BASED COGNITIVE BEHAVIOURAL THERAPY FOR POSTNATAL DEPRESSION


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Aim and Background: Although symptoms of depression have been shown to be reduced through internet interventions, no research has examined the efficacy of internet-based treatment of postnatal depression (PND). We report on the development of an internet intervention for PND (MumMoodBooster) which aims to reduce symptoms of depression and anxiety.

Method: Development of the intervention was achieved through an iterative process (culminating in systematic usability testing). We conducted formative research using focus groups with postpartum women to adapt the content, structure, and design of the successful Getting Ahead of Postnatal Depression intervention. The resulting MumMoodBooster intervention embodies the key Cognitive Behavioural Therapy elements that have been found to be effective in our PND face-to-face intervention as well as including a library of partner and infant modules, a web forum and telephone support. The final phase of development was systematic usability testing. Once functioning program components were created, 22 participants in Australia and the USA were recruited to a “think-aloud” procedure to test user-system interactions. Measures included the System Usability Scale, the Computer Self-Efficacy Scale and items adapted from the Technology Acceptance Model.

Results: Preliminary results reflected good acceptability and usability. The MumMoodBooster intervention is now being evaluated in a feasibility trial with 50 women.

Conclusion: The MumMoodBooster is an internet based therapy for PND that has the potential to increase treatment uptake and accessibility, and addresses the unique needs of depressed perinatal women, including infant and partner difficulties.
CHARACTERISING THE MEDICATION REGIMENS OF CONSECUTIVE PATIENTS PRESENTING TO AN EMERGENCY DEPARTMENT: DO PHARMACISTS NEED TO SEE THEM ALL?

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Background: Transitions of care such as emergency department (ED) presentation are high risk for medication misadventure.

Aim: To describe the medication regimens and medication misadventure risk factors for patients presenting to ED, to assist with determining the pharmacist work-force required.

Methods: Prospective cohort study of consecutive adult patients presenting to Austin Health ED during six pre-determined 4-hour periods between 8am–6pm, Monday to Saturday. A comprehensive medication history was documented by a pharmacist or pharmacy student on the hospital's ‘Medication on Admission’ form. The Australian Commission on Quality and Safety in Health Care Medication Risk Identification list and Prince of Wales Medication Risk Assessment (POWMRA) were completed.

Results: 173 patients were included (87% of adults presenting during allotted times); mean age 56.4±20.3 years, 44 (25%) admitted to an inpatient ward and 29 (17%) to the short stay unit. 34 (20%) patients took no regular medications prior to presentation, while 74 (43%) took ≥5 medications daily. One third of patients were unable or ‘borderline able’ to describe their medication history. 23 (13%) patients had a medication-related presentation. 36 (21%) took ≥1 high risk medications. According to POWMRA, 40 (23%) patients should be seen by a pharmacist.

Conclusions: Our ED has approximately 200 presentations daily. This study suggests that over 40 patients should be seen by a pharmacist due to the complexity of their pre-presentation medication regimen; many more than our current clinical pharmacy service sees. Additional pharmacist positions and innovative models of practice are needed to minimise risk of medication misadventure.

‘SMOKE-FREE’ HOSPITALS - HOW ARE WE GOING PROVIDING SMOKING CESSATION SUPPORTS TO OUR IN-PATIENTS?

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Aim: To investigate the extent of provision of smoking cessation interventions and supports to in-patients in three hospitals with "smoke-free" policies, and explore barriers to wider implementation.

Methods: A cross-sectional study of adult in-patients, who were current smokers, at three tertiary-referral hospitals with established smoke-free policies. A questionnaire was developed to obtain demographic details, information about past quit attempts, nicotine dependence, readiness to quit and smoking cessation supports offered in hospital. Patients were interviewed by a trained research assistant at least 48 hours after admission. A doctor, nurse and pharmacist involved in the patient's care were then interviewed to determine the smoking cessation supports they had/planned to provide and barriers to providing more extensive supports.

Results: Participants (n =167), mean age 50.8±15.2 years, started smoking at 16.4±5.6 years. 67 (40.1%) patients admitted to smoking since hospitalisation. 17(10.2%) patients had an assessment and documentation of their smoking status and plan in hospital. 73 (43.7%) patients had been offered pharmacotherapy to assist with quitting; of these, 43 (58.9%) had accepted this offer.

Reasons for not offering smoking cessation supports included lack of staff awareness of patient's smoking status or nicotine replacement product availability, other clinical issues taking greater priority, lack of education/confidence in initiating smoking cessation therapies and non-availability of a smoking cessation specialist.

Conclusions: Many patients are not receiving smoking cessation supports in hospital. Recommendations include; improved smoking status documentation, increased use of screening and monitoring tools and having specialist staff available to guide ward staff, especially when first-line therapies are declined.
A STABILITY STUDY OF METARAMINOL IN PREFILLED SYRINGES

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Background: Metaraminol 10mg/mL injection is often diluted with sodium chloride 0.9% and pre-drawn into syringes by anaesthetists for the management of intra-operative hypotensive crisis. There are a number of issues with pre-drawing drugs such as metaraminol in theatre, including the potential for administration errors and wastage.

The 10mg/mL ampoule presentation poses a significant safety hazard since the entire content needs to be drawn into a syringe and diluted so that 0.5mg aliquots may be administered. There have been incidents where 10mg rather than the intended 0.5mg have been administered to the patient. Local data suggests that around 60% of pre-drawn metaraminol is not administered, which represents significant wastage.

A stable, prefilled syringe presentation of metaraminol is likely to improve patient safety and reduce wastage.

Aim: To determine the stability of metaraminol 3mg/6mL prefilled syringes.

Methods: Metaraminol 10mg/mL injections were diluted with sodium chloride 0.9% and repacked into 3mg/6mL (0.5%) syringes. Syringes were stored at 3 different conditions: room temperature, refrigerated and frozen. Metaraminol syringes from each storage condition were analysed in triplicate, using a validated high performance liquid chromatography assay on days 0, 1, 7, 14, 28, 58, 91 and 126.

Results: Metaraminol 3mg/6mL syringes from all three storage conditions were stable when analysed to day 126 with levels remaining within ±1.83%, ±1.08% and ±2.45% of initial concentration for room temperature, refrigerated and frozen storage, respectively.

Conclusions: Metaraminol 3mg/6mL prefilled syringes were stable for at least 126 days when stored at room temperature, refrigerated or frozen.

IV PARACETAMOL ON IMPREST- KEEPING IT SUSTAINABLE

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Aim: To investigate concordance with hospital guidelines for ward-based intravenous paracetamol usage and explore nurses’ decision-making in selecting route of paracetamol administration.

Method: Patients prescribed paracetamol on one surgical ward (where IV paracetamol is available on imprest) were prospectively identified over two consecutive 3-day periods in October 2010. Data was extracted from patient charts using a structured data collection tool. Concordance with hospital policy was defined as Acute Pain Services involvement, or enteral/rectal routes being contraindicated.

Nurses on the same ward were surveyed over a two week period in March-April 2011, to explore their decision-making with respect to paracetamol orders that included multiple routes of administration. The questionnaire consisted of 3 questions pertaining to a patient scenario.

Results: 65 patients from 8 surgical units were included (median age 62 years). 43 patients were prescribed IV paracetamol. Only 14/65 (22%) patients had clear documentation that paracetamol was administered IV. For 13/14 (93%) patients, IV paracetamol usage was non-concordant with hospital guidelines; 8/14 (57%) patients concurrently received other medications orally.

The nurses’ survey (response rate 53%) found wide variability in terms of what ‘nil by mouth’ means with respect to medication administration as well as a perception of apparent superiority of IV paracetamol.

Conclusions: A significant number of patients received IV paracetamol outside hospital guidelines. Further projects are planned to achieve greater consistency around ‘nil by mouth’ and medication administration. An education intervention is indicated that highlights the equivalent efficacy of the various routes of paracetamol administration and encourages appropriate decision making.
AN AUSTIN BY DESIGN PROJECT: OBSERVATION OF LUNCH MEAL EXPERIENCE ON AN ACUTE HOSPITAL WARD.

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The prevalence of malnutrition in an Oncology ward was 72%. Protected mealtimes is an initiative that addresses barriers to meal access that may contribute to malnutrition. We aimed to describe the current mealtime environment, to identify barriers to meal access and develop specific local strategies to improve the mealtime experience. Redesign methodology including observation, process mapping, and root cause analysis was used to determine specific local barriers to food access. Service of 32 lunches was observed. Twenty-two percent of meal trays were out of reach; 80% of bedside tables were too cluttered for meal delivery; 59% of meals were interrupted and of these 37% of patient lunches were interrupted by menu monitors. It was unclear whose role it was to position patients and tables for meals, and to ensure there was room for placement of meal trays. Menu monitor interruptions were due to a change in workflow with a new electronic meal ordering system. Interventions included modification of menu monitor work-flow; hourly nursing rounds to address patient position and proximity, and inclusion of meal-time set up and assistance in job descriptions of Health Assistant Nurses. Evaluation of the impact of these changes showed tray out of reach increased to 28%, bed side table being cluttered reduced to 25% and total interruptions increased to 81%. The number of patients offered assistance increased. Further work will be done on the implementation strategies.
ISBAR – A STANDARDISED TOOL FOR COMMUNICATION
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Background: Ineffective clinical communication places the patient at an increased risk of adverse events. To improve clinical communication at Austin Health a standardised communication tool, ISBAR (Identify, Situation, Background, Assessment, Request) was introduced as a pilot study into the Emergency Department. Adapted from the SBAR tool (developed from the US Navy) it is a structured method of communication used in high reliability industries such as air traffic control and nuclear power.

Aim: To improve the quality of clinical communication in the Austin Health Emergency Department through the implementation of ISBAR as a standard communication technique for all clinical communication.

Method: Clinical staff in the Emergency department received ISBAR education sessions and visual tools in February, 2011. Post-education evaluation occurred in March, 2011, via staff survey and direct observation.

Results: Pre implementation findings identified <20% of staff discussed vital signs during clinical communication and only 22% of people gave recommendations for future treatment. After a 4 week period staff felt that the use of ISBAR decreased the likelihood of communication based errors.

<table>
<thead>
<tr>
<th>Elements of ISBAR used</th>
<th>Prior to ISBAR training</th>
<th>After ISBAR training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduce themselves by name</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>State their position</td>
<td>31%</td>
<td>60%</td>
</tr>
<tr>
<td>State the urgency of the situation</td>
<td>32%</td>
<td>63%</td>
</tr>
<tr>
<td>Give a clear explanation of the presenting condition?</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>Give relevant medical history?</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td>Explain the lead up to the situation?</td>
<td>77%</td>
<td>73%</td>
</tr>
<tr>
<td>Discuss the provisional diagnosis?</td>
<td>86%</td>
<td>96%</td>
</tr>
<tr>
<td>Advise what they have done for the patient?</td>
<td>71%</td>
<td>96%</td>
</tr>
<tr>
<td>Discuss test performed and findings available?</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>Mention vital signs?</td>
<td>16%</td>
<td>70%</td>
</tr>
<tr>
<td>Make it clear what was required of the receiver?</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>Advise of recommendations for further treatment?</td>
<td>22%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Conclusions: ISBAR brings a standardised approach to clinical communication which ensures vital information is consistently provided; and was well received by staff in the Emergency Department at Austin Health. Future plans are to implement and evaluate ISBAR to a range of settings across Austin Health with the aim to improve the safety and consistency of clinical communication.
CREATING A VOLUNTEER WORKFORCE AND TRAINING PROGRAM TO SUPPORT THE ADVANCE CARE PLANNING PROCESS

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Introduction: As the population ages there is an increase in the need to bring advance care planning (ACP) to the community's attention. Limited resources have led us to develop a program using volunteers to raise public awareness through group presentations.

Aim: to create and pilot a structured volunteer program using a professional volunteer workforce to provide ACP education to community and outpatient groups.

Process: A needs analysis was completed, along with identification of gaps within our service. A volunteer selection, screening and training program were developed. Themes addressed in training included:

- ACP and the process of coordinated ACP
- Public Speaking
- Answering difficult questions
- Using available resources

Results: Following training, volunteers began presentations to service clubs (e.g. Rotary, Apex), church groups, and outpatient rehabilitation groups. Evaluation on each stage of the project occurred. Ongoing support and performance assessment of volunteers occurred to maintain quality standards and ensure that the presentation remained focused on ACP.

Conclusion: This pilot project demonstrates the ability to create, within existing infrastructure, a volunteer program to deliver the ACP message to the community. This process has highlighted a broader potential for volunteers to facilitate specific ACP assistance. The community ownership of the volunteer program means that the ACP needs of the community are being heard and addressed and solutions are being created within the community.

A FILM TO DIGITAL CONVERSION FOR ULTRAVIOLET REFLECTANCE PHOTOGRAPHY OF THE SKIN

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Background: Ultraviolet (UV) reflectance photography is photography outside the visible, using specialist photographic equipment and film to capture an image in the 320nm–380nm, or UV-A range. The benefits of UV photography are significant to Dermatologists, but film based UV photography is tedious to perform and therefore rarely done.

Aim: To convert an analogue system of ultraviolet reflectance photography to a simplified digital technique. Explore the use of the Baader “Venus filter”, used in astronomical photography, in customizing a camera for UV photography.

Method: A range of lenses and lighting equipment were tested for suitability for UV photography. A Nikon camera was converted to a dedicated UV camera by fitting the Baader Venus filter internally. The converted camera was tested in a clinical setting by photographing the skin of several volunteers. Standard clinical images were then compared with the UV images to determine the success of the digital UV technique.

Results: Overall, UV photography showed pigment in greater detail than normal colour and black and white images. There were significant benefits using a converted digital camera. This improved camera sensitivity recording further into the UV-A region and an immediate preview of the image allowed for instant adjustments to correct for poor exposures, focus problems or patient movement. A standard glass lens and standard studio flash kit were found to be capable of recording images in the UV range.

Conclusion: This project was successful in converting a tedious rarely used film based technique into a simple, easy to use, patient friendly, digital workflow. The technique is used more often in the photography studio and has improved the range and quality of images taken in a clinical setting, providing another diagnostic tool for Dermatologists.
EMERGENCY CALLS TO SWITCHBOARD: A QUALITY IMPROVEMENT PROJECT
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There are over 3,500 emergency response calls per year at Austin Health. It was the practice at this and other hospitals that switch staff managed these calls by relaying exactly the information given by the caller eg “Respond Blue ward 8 west.” No specialised training was available. The Resuscitation Committee noted incident reports which highlighted communication deficits arising from this approach, resulting in the responding teams going to the wrong location.

In the interest of quality and safety the Resuscitation Committee and Communications Department developed an improved Switchboard Emergency Call Receiving Process and specialised training for switch staff.

The new call receiving process incorporates three steps: Verification, Confirmation and Communication of the emergency. On calling 7777, switchboard staff ask the following questions and then confirm the information with the caller:

What is your emergency?
What is your location?
Any specific questions related to each response.

The 4 hour training program developed in conjunction with the Victorian Employers Chamber of Commerce and Industry (VECCI) covers the background for the introduction of an emergency call receiving process, the three step flowchart, the different emergency codes, and the management of difficult calls.

The introduction of a prescribed call receiving process and specialised training for staff has been received positively. It is expected that this quality improvement will reduce the potential risk of miscommunication and confusion which can contribute to a delay in the emergency team's response. The principles covered within the training have the added benefit of being applicable to both emergency and non-emergency calls at Austin Health.

REPORTING OF INCIDENTS BY DOCTORS IN A MAJOR TEACHING HOSPITAL: AN AUSTRALIAN EXPERIENCE
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Background: The involvement of doctors in quality and safety has been demonstrated to be beneficial for patient care [1], however doctors are reticent to embrace incident reporting systems, reporting only 2.9% of incidents in a US study and tended to report more severe cases. [2] The trends in reporting of hospital incidents by doctors in Australia has not been reported in the literature to date, particularly whether there are any trends in incident type, severity or who reports incidents,

Aim: To document the incident reporting patterns of doctors within a major teaching hospital within Australia, to identify:

types of incidents reported (including severity of outcome)
groups of doctors with higher reporting rates
whether there are any differences in the reporting of incidents from residents, registrars or consultants.

Method
Audit of voluntary incident reporting system (Riskman) reported by doctors for 2009/2010 financial year.
Results: There was 152 incidents reported by doctors in 2009/10 (1.6% of all incidents).
115 different doctors reported incidents (20 doctors reporting multiple incidents, one doctor reported 9 incidents).
Anaesthetics (28 incidents) and General medicine (23 incidents) were most common units, with Operating suites the most common location (33 incidents).
No ISR1 incidents, only 10% ISR2 (some level of patient harm), 32% ISR3, 45% ISR4 (minimal harm).

Trends in types of incidents included: diagnostic investigation related, procedural or communication issues. Consultants tended to report more procedural and communication issues, whereas registrars reported more incidents relating to diagnostic investigations. Residents most commonly reported bloodborne fluid exposure incidents.

Conclusions: From this audit, medical staff tend to report incidents relating equipment, procedural or communication issues, but few incidents relating to complications or medical management issues. More senior doctors report incidents. Anaesthetics is an exemplar unit regarding reporting, likely due to senior leadership, a profession embracing safety, but also a procedural area with high risk.

JUNIOR DOCTORS EMBRACING QUALITY: CLINICAL RISK REGISTRAR

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Background: Medical staff engagement is essential for successful quality improvement. In Australian public hospitals, junior doctors provide a large component of patient-care, and are therefore essential to engage in the quality process.

Aim: To establish a hospital Clinical Risk Registrar position to increase medical input into clinical risk, increase exposure of junior doctors to quality improvement, and increase the quality profile within the medical profession.

Method

Collaboration with Emergency Department, Chief Medical Officer and Quality Unit to develop a 20 hour per week position for 6 months as a formal rotation from the Emergency Department Registrar pool. Provisional Accreditation of the position from ACEM was achieved for 12 months (2 rotations) with formal evaluation by the college in December 2010.

Results: The key roles of the Clinical Risk Registrar include:

- Assist clinical risk team with critical incident reviews
- Active exposure to clinical risk structures
- Junior doctor education in clinical risk
- Develop skills in clinical risk (Coronial processes and Root Cause Analysis methodology)

Following a 12-month evaluation, the position was College accredited. Internal evaluation currently pending (due to complete July 2011) of qualitative evaluation of individual registrars within the role and qualitative evaluation of Clinical Risk team of the contribution of the role to quality and safety.

Conclusions: The Clinical Risk Registrar role has become an integral part of the clinical risk team, both facilitating increased medical input to quality improvement initiatives, as well as providing a link for the junior and senior medical staff with quality improvement throughout the organisation, and broadly increasing clinician engagement in quality. The role is an exemplar for other organisations wanting to increase junior doctor involvement in quality.
EARLIER ACCESS TO STROKE UNIT CARE: IMPLEMENTATION OF A FAST-TRACK STROKE (FTS) PROTOCOL WITHIN AN ESTABLISHED AUSTRALIAN STROKE SERVICE – QUALITY PROJECT

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Background
Stroke unit (SU) admission within three hours of onset has been recommended but is difficult to achieve. To expedite SU admission from the emergency department (ED) at Austin Health (AH) a Fast-track Stroke (FTS) protocol specifying time-critical and non time-critical pathways was developed. Eligible patients receive IV thrombolysis in the SU rather than ED.

Aims
Three goals were proposed; 1) reduce median door-to-needle (DTN) time (alteplase-eligible stroke patients), 2) reduce median time to SU admission (clinically stable stroke patients) (aims: time-critical ≤ 30 minutes, non time critical ≤ 3 hours) and 3) improve ED patient flow.

Methods
Development of the FTS protocol was overseen by a steering committee with representation from multiple AH departments and disciplines and Ambulance Victoria. FTS inclusion/exclusion criteria (including clinical stability criteria) were incorporated and a staff education package rolled out. Evaluation compares patient outcomes and time delays (consecutive stroke presentations to ED) in the pre and post implementation periods, and considers organisational impact and staff satisfaction.

Results
FTS was implemented in November 2010 with post-implementation data collection concluding in June 2011. Of 350 post-implementation stroke presentations, 193 (55%) met FTS eligibility criteria, 126 (36%) were ineligible and 31 (9%) could not be fast-tracked due to bed-block. Of those ineligible, 15 (12%) were clinically unstable, 80 (63%) had an uncertain diagnosis or fully resolved symptoms and 14 (11%) presented outside of project operating hours. Timeframe aims were achieved for 35 (18%) eligible patients. Median door-to-needle time (patients thrombolysed in the SU) was 58 minutes.

Discussion
A FTS protocol expediting early admission to the SU for acute care and thrombolysis is safe and feasible, and has the potential to reduce time delays in acute stroke care.
CORRECT PATIENT, CORRECT IDENTIFICATION: AUDIT OF CLINICAL PRACTICES FOR MANAGING PATIENT IDENTIFICATION LABELS

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Background: Significant adverse events can arise from incorrect patient identification. Recent implementation of the WHO checklist identified an increase in the number of patients presenting to the operating theatre with incorrect patient identification. Although electronic diagnostic and medication ordering will reduce the risk within the organisation, a complete electronic health record is still many years off.

Aim: To determine:
- extent within organisation of incorrect patient labels
- severity of known incidents (ISR1/2)
- Whether a local culture/practice issue within the wards may be contributing to the risk of mislabelling patient identification.

Method: Analysis of all incidents in Riskman for 2010 "Incorrect ID, Incorrect information" for location, incident type and severity

Observations: Audit of local practice within clinical areas (8 wards, including ED) for storing, accessing and utilising patient labels.

Results: 28 incidents throughout 2010 (2 ISR3, 20 ISR4, and 6 Near Misses) of incorrect labelling of patient medical notes. No incidents of patient harm:
- 14 incidents in Operating Suites, 6 incidents in endoscopy suites, 2 Radiology
- Patient units: Gastroenterology, Orthopaedic Surgery, ENT, Plastic Surgery, Urology
- Ward areas: 8 North, 5 East, 5 North and 6 East

It is likely that the risk is across the organisation, (as WHO checklist will only identify surgical patients). Observational audit of ward areas identified inconsistent practices of storing and accessing patient identification labels (all wards stored labels in patient files, but some also in bed-side charts). In addition, most wards also had a centralised folder with all ward patient labels, either by bed number or alphabetical. Although these folders were meticulously managed by the ward clerk during hours, after hours admissions/ discharges were variable.

Conclusions: This audit demonstrates that local culture and practice creating work-arounds can impact on patient risk. Findings of audit presented to Clinical Outcomes Review Committee and Nursing, with strategies to improve consistency with managing patient labels in ward areas in progress.
CLINICAL REVIEW PANELS: MULTIDISCIPLINARY VIEW ON SAFETY
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Background: Reviewing clinical incidents is essential to learn from error. In our hospital, incidents were only reviewed in professional/program silos.

Aim: To develop a hospital-wide Clinical Review Panel to analyse cross-program, cross-professional serious adverse events, and develop practical, tangible recommendations for improved patient care.

Method: Clinical Review Panel established October 2010, adapted from Southern Health model. Involves monthly case reviews with medical (surgeons, physicians, intensivists, emergency, anaesthetists, diagnostics), nursing, allied-health, and pharmacy (with additional experts as required). Care management issues and recommendations developed utilising 2 best-practice frameworks [1]. Implementation of recommendations monitored through hospital’s clinical governance framework.

Results: A total of 7 Clinical Review Panels have been convened, reviewing 11 individual cases, one mini-cluster of cases (Ward 10 admissions), and one major cluster review (Inpatient Falls). Issues addressed within the cases have included:

- Falls incidence, prevention, and harm minimisation (cluster review)
- Failures of admission to Ward 10 (Aged care ward) (mini-cluster review)
- Unrecognised clinical deterioration (within surgical wards)
- Urgent medical review within Mental Health
- Trauma response within the organisation
- Transfers from acute to subacute

Recurrent trends in care management issues highlighted by the cases include: poor communication, failure of recognition of clinical deterioration, failure of escalation of clinical issues, failure to call MET when criteria met.

Qualitative analysis of panel members views, and progress with recommendations is currently pending (due to be finalised August 2011), however early anecdotal feedback strongly supportive of committee process and outcomes.

Conclusions: Early evaluation of the Clinical Review Panel has proven valuable as a tool to assist clinicians review cross-professional, multi-disciplinary incidents, and increase engagement of clinicians within quality and safety.


IMPROVING COLONOSCOPY BOOKINGS FOR OUTPATIENTS: AN AUSTIN BY DESIGN PROJECT
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Patients who require an urgent Colonoscopy wait to be contacted via telephone to be informed of their booking date. Patients become very anxious waiting for a booking confirmation and are often waiting by the phone. Patients who attend outpatient clinic leave without a Colonoscopy date as no booking staff attend the clinic.

It takes an average 7.5 days to be contacted by the Austin via telephone. Complex instructions are given over the phone, with varied results due to language barriers and level of patient comprehension. Bowel preparation and instructions are mailed out to the patient once booked. Patient often needs to come back to hospital for routine pre-op tests.

The goal was to have 100% of urgent Colonoscopy patients leave their Gastroenterology outpatients appointment with a booking date.

Existing staff was re-organised so that two nurses attended each clinic. We negotiated with outpatients to have designated rooms. We set up a Mobile booking office containing stock of brochures, medication etc. which was taken to clinic. The appointment template was modified to avoid late finish of clinic. All patients were given detailed booking information by a nurse, utilising carers, family members and interpreters. Pre-op tests were completed. It was well accepted by consultants. Non urgent colonoscopies attending their out-patient appointment with carers/interpreters are also being booked. Patient anxiety is reduced, as they know their booking date and who to contact. Patients avoided a second visit to do pre-op tests. Cost neutral – existing resources reorganised.

100% urgent colonoscopies are booked on the day of their outpatient appointment. Patient journey reduced from 7.5 days to 29 mins. Nurse booking time reduced from 494 minutes to 11 minutes (due to extended times between trying to contact by phone and the discussion taking longer by phone). Reduced urgent referrals in office and filing reduced.
MAKING HEALTH CHOICES: ADVANCE CARE PLANNING IN AGED CARE PROJECT

R. Sjanta, R. Fullam, L. Jackson

Respecting Patient Choices, Austin Health, Heidelberg, Australia

Objectives: The Respecting Patient Choices ‘Making Health Choices’ project is a pilot implementation and evaluation of a sustainability based model of advance care planning (ACP) in Residential Aged Care Facilities (RACF) in Victoria. The project is run in collaboration with Palliative Care Australia and is funded by the Commonwealth Department of Health and Aging. This presentation will focus on the outcomes and conclusions arising from the model evaluation.

Methods: Nineteen individual RACFs, representing 12 Aged Care organisations were selected from regional and metropolitan areas of Victoria. Three full-day workshops were held over a 6 month period, with RACFs expected to complete sustainability oriented tasks in between each workshop. The model is currently being evaluated through the use of pre and post implementation surveys designed to assess implementation related changes in organisational policies and practices, and staff knowledge, attitudes and behaviours, around advance care planning.

Results: The pre-implementation organisational survey revealed heterogeneity across organisations in the nature and quality of existing policies and practices around ACP. The pre-implementation staff survey revealed disparities between staff perceptions of their skill and confidence in conducting ACP conversations and findings relating to the accuracy of their ACP knowledge and attitudes towards ACP. We will present data on post implementation changes to these and other key findings.

Discussion: The findings of the evaluation to date will be discussed in terms of ACP sustainability, future education models and in the context of systemic challenges facing the Australian Residential Aged Care sector.

Contribution to the evidence base: Evaluation of the effectiveness of ACP implementations in Australian RACFs is an emerging area of research. This presentation will provide insight into the ability of a tailored ACP education and implementation model to produce significant shifts in staff knowledge attitudes and behaviours, and institutional policies and procedures around ACP. The key findings from this project will enable the development of refined models for the implementation of quality ACP within the aged care sector.

THE INTERN EXPERIENCE IN GENERAL MEDICINE: AN ‘INTERN LOG-BOOK’ TO IDENTIFY AND MONITOR TRAINING NEEDS.

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Background: General registration by the Medical Board of Australia requires medical graduates to complete an ‘internship’ where ‘structured experiences’ consolidate and extend theoretical knowledge and technical skills. Each intern post is accredited by the Post Graduate Medical Council of Victoria. However, determining if individuals appointed to those posts achieve the goals stipulated by the PMCV is not usually assessed.

Methods: Survey questions were determined by consultation with general physicians who have responsibility for intern supervision. Interns self-reported into a Microsoft Excel spreadsheet each week of their General Medicine rotation. Responses were collated via email. Validation of intern responses was determined by separately surveying other members of the General Medicine workforce.

Results: Logbooks were completed by 50/50 interns rostered to General Medicine posts over a 12 month period. Data reported by interns was consistent with reports of activities by other medical staff. Interns performed an average of 13.5 admissions (range 4 to 30) per rotation. There was a significant difference between the number of admissions performed by each unit, ranging from Med 5 (0.91/week) to Med 4 (2.20/week). The log-book identified that substantial time was expended by interns on database entry. Modification to the computing program was associated with a reduction in this time (26.93-11.17 minutes/week).

Conclusions: Internship experiences can be reliably monitored by self-report. This can provides a mechanism for determining the suitability of experiences during internship and for developing initiatives to improve the education value of internship.
REVITALISING FALLS PREVENTION AND HARM MINIMISATION: A MULTIDISCIPLINARY, CLUSTER REVIEW

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2Emergency Department, Austin Health, Heidelberg, Australia

Background International literature recognises inpatient falls as one of the leading causes of morbidity/mortality for hospital patients [1]. Despite utilising best-practice risk-assessment, our hospital's falls incidence remained static. Aim To undertake a retrospective review of inpatients falls severity and characteristics at a large Australian tertiary hospital, using incident reporting data. In particular, to determine potentially reversible factors for future risk-reduction strategies to reduce falls (i) incidence and (ii) severity. Method All reported incidents of inpatient falls from July 2007-October 2010 were audited for: unique falls identifier, severity, patient demographics (age, gender, admission diagnosis and admitting unit) and circumstances of fall (location, time, presence of an attendant). In addition, targeted cases reviews (using a modified IHI Injurious Falls Data Collection tool) audited falls risk-factors and mechanism-of-injury, comparing falls with minimal harm (ISR3/4) and severe harm (ISR1/2). Results A total of 6125 falls occurred (82% ISR4; 13% ISR3; 3% near-miss, 2% ISR2; and 0.2% ISR1). Patient demographics: male (59%); mean age 70 yrs (80yr mean for ISR1); units with highest absolute numbers of falls were Aged Care, General Medicine, Oncology and Palliative Care. A statistically significant peak of falls occurred at 10am (p<0.001). Additional findings from 40 case reviews: • Risk factors: 50% patients had previous fall, 60% cognitive impairment, 60% >2 medications assoc with falls, 65% on anticoagulants, >50% incontinent. Mechanism-of-injury: 50% associated with toileting • Of ISR1 falls (deceased), 90% had >2 medications associated with falls (sedatives, anti-hypertensives, antiparkinsons), 70% had cognitive impairment, and 70% associated with toileting Conclusion Results were reviewed by a multidisciplinary panel (medical, nursing, allied-health, pharmacy). Key recommendations include: nurse rounding (to address toileting); improved risk assessment (focusing on medications rationalisation); and environmental analysis. The relevance of admitting unit for falls risk awaits work to control for overall patient number in each unit. Further work recommended into the 10am peak. The clarity of the patient experience of falls at Austin has reinvigorated our clinicians in falls prevention.


INPATIENT FALLS WITH SERIOUS HARM –WHO, HOW AND WHY:A CASE SERIES

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2Emergency Department, Austin Health, Heidelberg, Australia

Background A recent audit of inpatient falls within the organisation identified a small group of patients whose fall was associated with their death. It was unclear whether there were any trends in the patient characteristics, mechanism of injury, or post-fall management that may assist with future preventative strategies. Aim To document the patient characteristics, risk factors, mechanism of injury and post-fall management of those patients who died following an inpatient fall at a major Australian tertiary teaching hospital. Method Retrospective case review of all ISR1 (deceased) falls incidents within the organisation's incident reporting database from July 2007 to February 2011, utilising IHI Injurious Falls Case Review Tool. Results A total of 18 inpatient deaths associated with falls were identified, with 15 case files accessible for review. Patient demographics: mean age 81 yrs, 7 of 15 patients had a malignant co-morbidity. Of the patients without malignancy, 6 had multiple medical comorbidities (IHD, COPD), 2 were awaiting aged care placement, and one had significant post-surgical complications. Risk factors for falls: 12 patients on anti-hypertensives; 11 patients on medications with sedative effect. Mechanism of injury: 14 of 15 falls occurred unaccompanied; 11 of 15 falls occurred after-hours (after 5pm, before 9am); 7 of 15 falls were related to bathroom/toileting. Cause of death: 7 patients died from medical complications of fractured hips; 3 patients from intra-cerebral/subdural haemorrhage. 5 patients died within 24 hrs, with an average of 2 days. Risk factors for harm: 8 patient on anticoagulation. Conclusion Most inpatient deaths associated with falls occur alone, after hours, and relate to bathroom/toileting in an elderly population with multiple co-morbidities. The cause of death is more likely related to medical complications from fractures in patients with significant comorbidities. The clarity of severe inpatient falls at Austin has informed our risk reduction strategies and reinvigorated our clinicians in falls prevention.
PREDICTION OF SLEEP-DISORDERED BREATHING IN PREGNANCY
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2Perinatal Medicine, Mercy Hospital for Women, Heidelberg, VIC, Australia

Introduction: Upper airway obstruction during sleep may develop during pregnancy, with negative outcomes for the mother and foetus. Obstructive sleep apnoea (OSA) during pregnancy is often investigated using self-report questionnaires validated in predominantly male, middle-aged populations. This study examines the predictive value of two commonly-used questionnaires in a group of pregnant women.

Methods: Thirty-six pregnant women completed the Berlin Questionnaire (BQ) and the Multivariate Apnea Risk Index (MAPI) in the 2nd trimester (T2) and again at 37 weeks gestation (T3) at the time of having an overnight polysomnogram.

Results: OSA (AHI≥5) was found in 10 out of 36 (28%) women. (i) BQ: At T2, the BQ identified 24 women as high risk for OSA. Sensitivity and specificity in T2 for AHI≥5 were 90% and 42% respectively, with a positive predictive value of 38% and negative predictive value of 92%. Predictive ability of the BQ did not improve if completed at T3. (ii) MAPI: At T2, the predictive ability of the MAPI for AHI≥5 using the area under an ROC curve was 0.74. This increased to 0.79 after removing gender, age and BMI from the model. The predictive ability of the MAPI did not improve if completed at 37 weeks.

Discussion: The Berlin Questionnaire and MAPI are useful to rule out pregnant women without OSA, but are not able to identify those with OSA. Hence, utilising self-report measures alone in studies of sleep-disordered breathing in pregnant women is likely to result in significant inaccuracy in prevalence estimates and relationships to other outcomes.

OBJECTIVE AND SUBJECTIVE DROWSINESS INCREASES DUE TO BENZODIAZEPINES AND ALCOHOL CONSUMPTION AND IS ASSOCIATED WITH DECREASED DRIVING SIMULATOR PERFORMANCE.

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Introduction: Changes in eyelid movements occur in drowsy subjects, however less is known about changes in eyelid movements due to alcohol and legal drugs such as benzodiazepines. We measured changes in eyelid movements following sleep restriction, alcohol ingestion and benzodiazepines with Optalert™ Drowsiness Measurement System (ODMS), which uses infrared reflectance oculography to measure eyelid movements.

Methods: Participants (N=32) completed a 60 minute driving simulation task in a six condition randomised cross over design over three days at least one week apart. Conditions were 1) baseline, 2) 0.05% blood alcohol concentration (BAC), 3) 0.08%BAC, 4) 20mg Temazepam (Temaze), 5) the morning (SR-AM) and 6) afternoon (SR-PM) following sleep restriction to four hours. Drowsiness was assessed objectively by ODMS (Johns' Drowsiness Score (JDS), range 0-10). Participants rated subjective symptoms using the Sleepiness Symptoms Questionnaire (SSQ).

Results: JDS increased significantly from rested baseline due to alcohol and there was a trend towards increased JDS due to Temazepam. Linear regression found that increased mean and maximum JDS values are associated with decreased driving simulator performance (greater lane steering deviation) and increased subjective sleepiness (p<0.05).

<table>
<thead>
<tr>
<th>Condition</th>
<th>JDS(mean)</th>
<th>JDS (max)</th>
<th>SSQ</th>
<th>Lane variation(cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.2 (±1.6)</td>
<td>3.7 (±2.2)*</td>
<td>24 (IQR 14)</td>
<td>63.9 (±25.8)</td>
</tr>
<tr>
<td>0.05% BAC</td>
<td>2.9 (±1.4)*</td>
<td>4.7 (±2.1)*</td>
<td>35.5 (IQR 15)</td>
<td>79.4 (±36.3)*</td>
</tr>
<tr>
<td>0.08% BAC</td>
<td>3.5 (±1.8)*</td>
<td>5.2 (±1.9)*</td>
<td>39 (IQR 16)*</td>
<td>80.4 (±26.1)*</td>
</tr>
<tr>
<td>Temaze</td>
<td>2.8 (±1.8)</td>
<td>4.5 (±2.3)</td>
<td>31 (IQR 20)*</td>
<td>82.5 (±38.4)*</td>
</tr>
<tr>
<td>SR - AM</td>
<td>2.3 (±1.4)</td>
<td>4.2 (±1.9)</td>
<td>30.5 (IQR 19)*</td>
<td>68.0 (±26.2)</td>
</tr>
<tr>
<td>SR - PM</td>
<td>2.4 (±1.3)</td>
<td>4.3 (±1.9)</td>
<td>31 (IQR 20.5)*</td>
<td>69.6 (±28.2)*</td>
</tr>
</tbody>
</table>

* p<0.05 increase from baseline

Conclusion: Ocular measures of alertness (JDS) are altered by alcohol consumption and benzodiazepines in a dose response manner.
PERCEPTION OF DRIVING ABILITY IS IMPAIRED BY SLEEP ENHANCING MEDICATION.

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4Respiratory and Sleep, Austin Health, Heidelberg, VIC, Australia

Introduction: Alcohol, sleepiness and drugs are leading causes of road accidents. Temazepam is prescribed for short term treatment of insomnia and was the 6th most prescribed drug in Australia in 2000. MIMS consumer medication information advises individuals not to drive until they are aware of how Temazepam affects their driving ability.

Methods: Participants (N=32) completed a 60 minute driving simulation task in a six condition randomised cross over design over three days at least one week apart. Conditions were 1) baseline, 2) 0.05% blood alcohol concentration (BAC), 3) 0.08%BAC, 4) 20mg Temazepam, (Temaze) 5) the morning (SR-AM) and 6) afternoon (SR-PM) following sleep restriction to 4 hours. Participants rated their willingness to continue driving if in a real-life situation of a short suburban drive in traffic (SDQ1) and a continuous long distance drive (SDQ2).

Results: Participants’ driving ability, as measured by variation in lane position, was significantly worse than in a rested baseline condition in the 0.05%BAC, 0.08%BAC, Temaze and SR-PM conditions (p<0.05), but not SR-AM (p>0.05). Willingness to continue driving was compared to the percentage change in driving ability from a 0.05%BAC benchmark of driving safety using Fisher’s exact test. Perception of driving impairment was found to be underestimated in the Temaze condition with a substantial proportion of participants reporting willingness to continue driving despite their driving ability being deteriorated to a level greater than the 0.05%BAC condition (see Table 1).

<table>
<thead>
<tr>
<th>Performance</th>
<th>Temaze SDQ1</th>
<th>Temaze SDQ2</th>
<th>SR-PM SDQ1</th>
<th>SR-PM SDQ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.05%BAC</td>
<td>16%</td>
<td>16%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;0.05%BAC</td>
<td>26%</td>
<td>21%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 1: Proportion of participants reporting willingness to continue driving after performing better (<0.05%BAC) or worse (>0.05%BAC) than during a 0.05%BAC driving simulation (Fisher’s exact test, p<0.05)

Conclusion: Individuals do not accurately perceive their driving ability following Temazepam administration.
THE EFFECT OF SINGING ON RESPIRATORY AND VOICE FUNCTION FOR PEOPLE WITH QUADRIPLEGIA: A RANDOMIZED CONTROLLED TRIAL

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Aim: We aimed to examine the effect of a group therapeutic singing intervention on respiratory function, voice quality and mood in people with quadriplegia.

Method: Twenty-four participants with chronic quadriplegia (C4–C7, ASIA A & B) were randomly assigned to experimental or active control groups. The experimental group (n=13) attended group singing therapy three times weekly for 12 weeks. The control group (n=11) attended group music appreciation and relaxation for 12 weeks. Respiratory function tests, EMG and voice analysis were conducted pre, mid, immediately post and 6 months after both interventions. Mood and quality of life questionnaires and interviews were also performed at these time points.

Results: The experimental group demonstrated significant improvements in inspiratory muscle strength (p=0.001) which were maintained by the experimental group at the 6 month follow up (p=0.001). There was a tendency towards improvement in other measures of respiratory function for this group. An increase in sound pressure level and a greater ability to project voice over background noise over the assessment period were suggested for experimental group. Improvements in measurements of voice quality were also evident for the experimental group. Both groups demonstrated an improvement in mood (p=0.002) and this improvement was maintained by the music appreciation and relaxation group (control, p = 0.017).

Conclusion: Group music therapy can have a positive effect on physical outcomes, and can also improve mood, energy, social participation and quality of life for people with quadriplegia. Specific singing therapy can augment these general improvements by increasing inspiratory muscle strength.
THE 6-MINUTE WALK TEST ELICITS HIGH BUT SUBMAXIMAL CARDIORESPIRATORY RESPONSES IN INTERSTITIAL LUNG DISEASE

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The 6-minute walk test (6MWT) is used to assess exercise capacity and establish prognosis in interstitial lung disease (ILD), however the physiological load imposed by the 6MWT is unknown. This study compared cardiorespiratory responses to 6MWT and incremental cycle ergometry testing (CPET) in ILD.

Methods: 15 participants with ILD (nine IPF) with mean age 70 (standard deviation 12) years and TLCO 57 (17) %predicted undertook CPET and 6MWT on the same day in random order. Pulmonary oxygen uptake (VO₂), ventilation (Vₐ), carbon dioxide production (VCO₂), oxyhaemoglobin saturation (SpO₂) and heart rate were compared between the tests using a portable metabolic cart. Relationships between 6-minute walk distance (6MWD) and peak cardiorespiratory responses on CPET were evaluated using correlations.

Results: Peak VO₂ measured during the 6MWT was lower than during CPET (15.1 (3.5) vs 17.5 (2.6) ml.kg.min⁻¹, p=0.03). Oxygen consumption during 6MWT reached a mean of 87% of VO₂peak achieved on CPET (95% confidence interval 76-98%VO₂peak). Peak ventilation, carbon dioxide production and peak heart rate were significantly lower during 6MWT, but there was no difference in nadir SpO₂ (90 (4) % vs 91 (3) % on 6MWT and CPET respectively, p=0.14). A higher 6MWD was associated with a higher peak work rate (r=0.93, p<0.001) but there were no relationships between 6MWD and peak cardiorespiratory responses on CPET.

Conclusions: The 6MWT elicits a high but submaximal oxygen uptake in people with ILD. Given the poor relationship between peak cardiorespiratory responses and walk distance, the prognostic value of the 6MWT may be related to the degree of oxygen desaturation elicited by this test.

A PILOT, RANDOMISED CONTROLLED TRIAL OF RETINAL ARTERY FLICKER INDUCED VASODILATATION TO DETECT CHANGE IN ENDOTHELIAL FUNCTION IN SEVERE OSA.

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Obstructive sleep apnoea (OSA) is a common disease that is associated with significant cardiovascular risk (CVR) and endothelial dysfunction(ED). ED measured by flow mediated dilatation (FMD) can be reversed in OSA patients by CPAP. Retinal artery flicker induced vasodilatation (RAFIV) is a novel, non-invasive, accurate and reproducible method of measuring ED. This study assessed if RAFIV can detect a change in ED in patients with severe OSA and CVR factors treated with CPAP.n=29 OSA patients - AHI ≥ 30, with associated hypoxaemia – Sa O₂ <90% for ≥6% of total sleep time (%<90TST) with known coronary artery disease or two or more CVR factors were recruited. Baseline RAFIV and FMD were performed and repeated 6 weeks after randomisation to CPAP treatment or no treatment.Subjects were middle aged, 49.7(14.9) years, obese, BMI 40.5(10.5) with severe OSA, AHI 79.8(29.1) and %<90 TST 33.5 (21.3), 17 were male. ED was present at baseline with RAFIV 1.8% (1.6) and FMD 4.7% (2.3), but was not significantly correlated with AHI or measures of hypoxaemia. There was no significant change in RAFIV or FMD following 6 weeks of CPAP treatment. This study did not demonstrate that RAFIV can detect a change in ED in patients with severe OSA and CVR factors treated with CPAP. Also there was no significant change in FMD. Other studies have shown a change in ED after 6 months CPAP treatment. It may be that the duration of CPAP treatment in this study was insufficient. Also CPAP compliance was poor, 36% of CPAP users, met standard compliance benchmarks. Further studies with longer CPAP treatment periods and better compliance are needed to fully assess the utility of RAFIV to detect changes in ED in response to CPAP treatment of OSA.
LIGHT SENSORS FOR DETERMINATION OF LIGHTS OFF TIME IN HOME POLYSOMNOGRAPHY

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Introduction: Polysomnography (PSG) in the home has advantages over in-laboratory PSG, but one important disadvantage is the inability of current devices to record lights off (Loff) and on times and thus important indices such as sleep onset latency and sleep efficiency cannot be determined. This study evaluates the characteristics of a prototype light sensor (Compumedics) used with a portable PSG device (SomtePSG, Compumedics), and its utility in the home where light conditions are uncontrolled and it is impractical to calibrate the light sensor to the conditions in each individual home.

Methods: 3 examples of the light sensor were exposed to incandescent light at a range of controlled light levels to determine their signal characteristics. 24 home PSGs were analysed to explore the characteristics of the light sensor signal in the home.

Results: The table below shows the results for the sensor signal characteristics. The light sensor allowed a discernable Loff to be identified in 19 of 24 home PSGs, and in these 19, the mean difference between patient reported and light sensor Loff was 1.2 min (SD 16.6, range -23 to +50).

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Linear range (Lux)</th>
<th>Sensitivity (mv/Lux)</th>
<th>Drift (Lux) over 14 hours</th>
<th>Linearity (full scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensor 1</td>
<td>0 - 334</td>
<td>0.749</td>
<td>0.2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Sensor 2</td>
<td>0 - 382</td>
<td>0.655</td>
<td>0.1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Sensor 3</td>
<td>0 - 350</td>
<td>0.713</td>
<td>0.4</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Discussion: The light sensor signals were found to have good sensitivity and linearity, low drift and record a range of lux appropriate for the home setting. When used in home PSG, these light sensors were able to establish Loff in the majority of PSGs. The wide range of differences between patient reported and sensor Loff demonstrates the importance of objective determination of Loff in home PSG, particularly for studies where accurate measurements of Loff dependant indices such as sleep onset latency are needed.

CONTINUOUS POSITIVE AIRWAY PRESSURE REQUIREMENTS ARE LOWER IN THOSE WITH QUADRIPLEGIA AND OBSTRUCTIVE SLEEP APNOEA COMPARED WITH ABLE-BODIED INDIVIDUALS WITH OBSTRUCTIVE SLEEP APNOEA.

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Objective: to compare CPAP requirements between OSA patients with quadriplegia and those who are able-bodied. Study Design: population-based retrospective case-control study.

Subjects: able-bodied and quadriplegic individuals attending the Austin sleep lab in 2009. Measures: Diagnostic and CPAP titration polysomnograms of able-bodied individuals and those with quadriplegia were reviewed for demographics, BMI, AHI and CPAP levels required to effectively treat obstructive sleep apnoea. Results: Polysomnograms from 16 individuals with quadriplegia and 253 able-bodied individuals were examined. There was no significant difference in AHI (p = 0.27) or BMI (p = 0.286) between the two groups however those from the able-bodied group were significantly older (p=0.02) and required significantly higher levels of CPAP to effectively treat their OSA (p <0.001) than those with quadriplegia. In able-bodied individuals there was a linear correlation between AHI and effective CPAP (r = 0.452, p <0.001) as well as between increasing AHI and BMI (r= 0.4, p<0.001) and between effective CPAP and BMI (r= 0.344, p<0.01). There were no such correlations found amongst those with quadriplegia and OSA. Amongst the able-bodied over two thirds (68.8%) required 10-16cmH20 to control their OSA and nearly one third required over 16cmH20 to control their disease. In contrast, amongst those with quadriplegia over two thirds (68.8%) required less than 10cmH20 of CPAP in order to control their disease.

Conclusion: Those with quadriplegia and OSA require significantly less CPAP to treat their OSA at any given AHI than those who are able-bodied. This observation is independent of BMI.
PATHOGENESIS OF OBSTRUCTIVE SLEEP APNOEA IN QUADRIPLEGIA

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Introduction: Obstructive sleep apnoea (OSA) is estimated to be 2 to 5 times higher in patients with quadriplegia than in able-bodied (AB) individuals. In order to better understand the causes of OSA in quadriplegia we aim to investigate upper airway function in quadriplegia. High nasal resistance predisposes to OSA in AB individuals. In patients with quadriplegia, the spinal sympathetic circuits lose tonic control and induce vascular engorgement of the airway causing the nasal mucosa to thicken. We therefore hypothesized that nasal (R\textsubscript{na}) and pharyngeal (R\textsubscript{ph}) resistance will be 1) elevated in patients with quadriplegia and OSA compared to AB individuals with and without OSA, and 2) reduced to AB levels with decongestant.

Methods: AB and patients with quadriplegia both with and without OSA are being recruited. Subjects are instrumented with epiglottic and choanal pressure catheters, a nasal mask and pneumotachograph. All measurements are performed while subjects are supine during wakefulness. R\textsubscript{na} and R\textsubscript{ph} (in cmH\textsubscript{2}O/l/s, calculated from mask, choanal and epiglottic pressures at a flow rate of 200ml/s), were determined for 5 minutes, before and 5-10 minutes after application of decongestant (0.5ml of phenylephrine 0.5%).

Results: One patient with quadriplegia (20 years old) and one healthy AB individual (45 years old) have been studied to date. The patient with quadriplegia showed elevated resistance at baseline (R\textsubscript{na}=6.26, and R\textsubscript{ph}= 5.29, compared to R\textsubscript{na}=2.43, R\textsubscript{ph}=1.05 in the AB). After decongestion, the R\textsubscript{na} was 1.51 in the patient with quadriplegia and 0.80 in the AB. The R\textsubscript{ph} was similar to baseline after phenylephrine.

Discussion: Although very preliminary, these data suggest that after quadriplegia the R\textsubscript{na} is particularly elevated. This is probably due to the partial loss of function of the autonomic nervous system. The high R\textsubscript{na} in patients with quadriplegia appears to be significantly reduced by the application of decongestant. The high R\textsubscript{na} and R\textsubscript{ph} observed are potentially one of the risk factors for OSA in quadriplegia but further data are required.

ROLE OF INPATIENT SPIROMETRY DURING EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in Australia and worldwide, and exacerbations are an important health outcome in patients with COPD. Spirometry is the gold standard for the diagnosis, assessment and monitoring of the disease, but its role during COPD exacerbations is unclear. The aim of this study was to determine the role of spirometry during admissions for COPD exacerbation.

Methods: Twenty patients with an admission diagnosis of COPD exacerbation were recruited into the study. Subjects were randomised into either group A or B and all subjects underwent daily lung function testing using a portable spirometer. Registrars caring for subjects in group A were provided the lung function results and asked to complete a survey regarding their views on the role of spirometry during exacerbations.

Results: Seventeen of the 20 subjects were able to produce at least one spirometric test fulfilling ATS/ERS acceptability criteria during their admission, and 15 of these subjects were able to do so within the first three days of admissions. No statistically or clinically significant changes in lung function were observed between admission and discharge. Results of the physician survey indicated that registrars found it desirable to have spirometry results available, but it did not seem to have any bearing on their management.

Conclusion: It is possible for sick patients to perform accurate and reliable spirometry during COPD exacerbations, and registrars indicated a desire to have these results. Inpatient spirometry seems to be a viable opportunity to obtain lung function.
A COMPARISON BETWEEN THE SENSITIVITY AND RELIABILITY OF EMG AND PIEZOELECTRIC SENSORS FOR MEASURING LIMB MOVEMENTS IN SLEEP.

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Introduction: 2007 recommendations by the American Academy of Sleep Medicine stated during sleep studies, limb movements should be measured using bilateral EMGs of the Tibialis Anterior. This recommendation is contrary to the previously widespread use of piezoelectric sensors. Few studies have compared the reliability and sensitivity of these measures. Aims: (1) To compare the sensitivity and specificity of piezoelectric and EMG sensors in a broad range of controlled leg movements, in a range of different measurement positions. Method: Six EMG electrodes and three piezoelectric sensors were placed on the right leg of two participants, in nine different positions on the leg. A series of standardised leg movements was performed. Average voltage increase was calculated for each movement-type set. Results: The piezoelectric sensors detected a broader range of leg movements types in both participants, regardless of their position. The voltage increase of the piezoelectric sensor when placed on the thigh, calf or foot varied between participants, with the thigh being the optimal position for detecting the movements of Participant 1, and the foot being the optimal position for detecting the movements of Participant 2. Of the EMG electrodes, the EDB muscle had the highest average increase above baseline for both participants. Conclusion: These preliminary results suggest piezoelectric sensors are more reliable and sensitive than EMG for measuring limb movements during sleep. The optimal EMG may be of the Extensor Digitorum Brevis rather than the Tibialis Anterior. Subsequent work will assess these measurements in more subjects as well as investigate the nature of leg movements during sleep.

(1) Iber C, Ancoli-Israel S, Chesson A, Quan S. for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications

GENIOGLOSSUS EMG RESPONSE TO THRESHOLD RESISTIVE LOADS IN SEVERE OBSTRUCTIVE SLEEP APNOEA VS. HEALTHY CONTROLS

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Introduction: The role of upper airway motor impairment in obstructive sleep apnoea pathogenesis is incompletely defined. In particular motor responses to respiratory loads spanning the threshold of conscious detection are not well studied. Responses to such loads may be important as an impaired response to minor upper airway threat may lead to worsening collapse. This study compared genioglossus EMG (EMGgg) responses to respiratory loads spanning conscious detection in severe OSA vs. controls. Methods: Sixteen untreated severe OSA patients (all with AHI >30 using Chicago criteria) and 16 age and gender matched healthy controls participated. Participants were awake, seated and had intramuscular EMGgg recorded. They wore a nasal mask connected to a resistive loading manifold, which supplied various resistive loads (approx. 1.2, 2.2, 3.0, 6.2 cmH2O/L/sec), as well as manifold occlusion and a zero load control. Loads were presented 90 times each during mid-inspiration, every 2-4 breaths and in a random block design. Participants were cued prior to stimulus presentation and signalled conscious detection with a button press. Results: A mixed-between-within subjects ANOVA compared peak EMGgg amplitude within 200ms of stimulus presentation between groups (OSA vs. control) across the 5 loading conditions. There was not a statistically significant main effect of group (P = 0.707) or interaction between group and load (P = 0.793). There was a trend for EMGgg amplitude to increase with increasing load magnitude (P = 0.052). These results however were possibly confounded by the novel finding of EMGgg suppression in response to loading in a proportion of participants; 81% of OSA and 63% of controls showing EMGgg suppression in response to at least 1 loading condition. Discussion: This preliminary analysis does not support systematic impairment of upper-airway motor response to threshold respiratory loads in OSA. The novel finding of EMGgg suppression in response to resistive loading requires further investigation.
CPAP ADHERENCE IN HOME VS IN-LABORATORY IMPLEMENTED PATIENTS

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Continuous Positive Airway Pressure (CPAP) is currently the treatment of choice for patients with moderate to severe Obstructive Sleep Apnoea. Home implementation of CPAP using an Automatic-CPAP (APAP) device to determine treatment settings is reported to be as effective as traditional in-laboratory studies. Aim: To compare initial take up and adherence rates between home-APAP patients and in-laboratory patients. Method: Forty three consecutive home APAP patients and 47 consecutive in-laboratory patients were called three months after their implementation study. Objective adherence data (machine usage) was obtained from patients still using treatment. Reasons for discontinuing treatment were also documented.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Home APAP Patients (n=43)</th>
<th>In-laboratory patients (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take up rates (%)</td>
<td>76</td>
<td>71</td>
</tr>
<tr>
<td>3 month adherence (%)</td>
<td>46</td>
<td>43</td>
</tr>
<tr>
<td>Mean usage (hours/night)(SD)</td>
<td>5.1 (2.2)</td>
<td>4.4 (2.5)</td>
</tr>
</tbody>
</table>

The main reason for not starting treatment amongst home APAP and in-laboratory patients was the inability to tolerate treatment. Conclusion: Overall, this study suggests that take up and adherence rates for home APAP implemented patients were at least as good as those for in-laboratory implemented patients.

PALLIATIVE PATIENTS FACING A MOVE TO RESIDENTIAL CARE: TOWARD A BEST PRACTICE MODEL

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AIM: Both internationally and locally the trend in specialist palliative care is to shorter stay, high-turnover palliative care units with limited access to end-of-life care, a controversial change with major implications for social work. Raising the issue of moving on to a nursing home can be emotionally fraught and stressful for patients and families, and frequently ends in the death of the patient rather than transfer to an aged care facility. The aim of this project is to examine outcomes for palliative patients facing residential care and to suggest a best practice model.

METHOD: A clinical data mining methodology was utilized to audit 68 palliative patients recommended for residential care from 2005 to 2011. By means of medical and ACAS records demographics, illness characteristics, final destination, and survival time were analysed.

DISCUSSION: This population of patients is elderly, about a third of CALD background, mainly cancer patients with longer prognoses. Since 2005 36% died before transfer to an aged care facility, half were successfully transferred, and 14% opted to return home rather than face a move to residential care. Patients transferred to an aged care facility survived on average for 3 months.

IMPLICATIONS: The results suggest a need for a more rigorous assessment process so we can consistently target appropriate patients, better support them through the transition to residential care, and minimise distress.
CREATING A PLACE FOR YOUNG PEOPLE IN AN ADULT'S WORLD
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Adolescent and young adults (AYA) with a cancer diagnosis often receive their treatment within a healthcare system developed for adult patients. As a result, the needs of young adults faced with issues such as emerging self and professional identity, developing sexuality and so on, can go unnoticed by cancer care professionals. The challenge for Social Work is to provide a targeted service to this small group with specific life stage needs, within a large general hospital.

This presentation will describe the results of a needs study, which explored the psychosocial needs of AYA patients receiving care at the Austin Hospital, Melbourne. A consecutive sample of twenty AYA patients aged 18-25, diagnosed during 2011, were invited to complete a questionnaire about their perceptions of supportive care services needed to promote survivorship. The focus of the questionnaire was to explore ways in which supportive care staff could promote AYA wellbeing and social connectedness, critical for emerging self identity.

Analysis of the results highlighted the key issues for AYA patients in this setting, which has influenced the delivery of supportive care services and establishment of the model of care in transition to the new Olivia Newton-John Cancer and Wellness Centre.

PREOPERATIVE METABOLIC PARAMETERS ON FDG-PET AS PROGNOSTIC INDICATORS FOR COLORECTAL LIVER METASTASES
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Background: Colorectal liver metastases (CRLM) are the major contributor to the mortality of colorectal cancer patients. Treatment for CRLM is associated with significant morbidity and must be tailored to the patient's risk of relapse and likely survival. However, tools developed in the past to risk-stratify patients have generally been limited in their prognostic capacities. This retrospective study aims to assess the prognostic utility of metabolic measurements derived from ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) compared to previously proposed prognostic scoring systems.

Methods: Preoperative, post-chemotherapy ¹⁸F-FDG PET/CT studies from a series of 30 patients who underwent liver resection for CRLM were evaluated. Quantitative ¹⁸F-FDG PET analysis calculated the mean and maximum standardised uptake value (SUVmean, SUVmax), metabolic tumour volume (MTV), and tumour glycolytic volume (TGV) as measures of tumour metabolic uptake. The predictive value of these measurements were compared to that of four prognostic scores proposed by Fong (MSKCC), Iwatsuki (Pittsburgh), Nordlinger, and Rees (Basingstoke).

Results: High MTV and TGV in patients before liver resection was significantly associated with poorer overall survival (P=0.001) and recurrence-free survival (MTV: P=0.001, TGV: P=0.002), whereas SUVmax and SUVmean did not exhibit significant predictive ability. Amongst the prognostic scores, prediction of outcome was most accurate using the Basingstoke index (Area Under Curve=0.898), while the Fong score was found to be a predictor of recurrence-free survival (P=0.034).

Conclusion: Assessment of metabolic tumour burden with FDG-PET parameters may simplify the prognostication of CRLM and be a valuable adjunct to current prognostic scoring systems.
THE EFFECTS OF AN ANTIHYPERTENSIVE DRUG, CAPTOPRIL, ON LIVER REGENERATION AND COLORECTAL CANCER LIVER METASTASES

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Introduction: Liver regeneration (LR) following liver resection (PH) for colorectal cancer liver metastases (CRCLM) may be associated with high tumour recurrence. We have shown that the renin-angiotensin system (RAS) is up-regulated during LR and an inhibition of the angiotensin-converting enzyme using captopril, significantly inhibited CRCLM. This study investigated the effects of captopril on LR and CRCLM following PH.

Methods: 70% PH and CRCLM models have been well established in our department. CBA mice were randomized to 70% PH and 70% PH with CRCLM. Liver specimens were collected on days 1, 2, 4, 6, 8 post-PH and also on days 16 and 21 (with CRCLM). The effects of captopril (750 mg/kg) were measured by liver-to-body weight ratio (LBW) and hepatocyte proliferation, apoptosis and size. Further measurements of liver stellate cell count and matrix metalloproteinase (MMP)-9 were also performed.

Results: Captopril did not inhibit liver regeneration. Captopril increased LBW on day 2 (0.57) compared to controls (0.49) but by day 6, captopril decreased LBW (0.5 compared to 0.73). LBW was similar between controls and treated by day 8. Interestingly on day 2, hepatocyte proliferation (3.4 compared to 53.7% for controls) and size (303.1 compared to 406.3 mm²) were decreased by captopril, while stellate cells (65.39 cells/100 000 mm²) and liver MMP-9 (0.68 units/mm²) were increased (controls having 48.08 cells/100 000 mm² and 0.12 units/mm²). Hepatocyte apoptosis was unchanged by captopril.

Conclusion: Captopril-associated improvement in LR is possibly attributed to stellate cells and MMP-9, and not changes in hepatocyte proliferation, apoptosis or size.

THE COUNTER-REGULATORY EFFECT OF AT1/AT2 RECEPTORS ON MACROPHAGE FUNCTION

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Introduction: Blockade of the renin-angiotensin system (RAS) inhibits tumour growth in several cancers, including colorectal liver metastases. The immunomodulatory potential of the RAS may, in part, be responsible for this anti-tumour effect. A majority of the RAS effects are mediated by the AT1 receptor while activation of the alternative receptor (AT2 receptor) has counter-regulatory effects. This study investigates the direct effects of the RAS on macrophage function in vitro.

Methods: P338D1 cells, a murine macrophage cell line, were treated with angiotensin II with either AT1 receptor blockade (Irbesartan, 1µM) or AT2 receptor blockade (PD123319, 1µM) for 24 hours. The protein expression of VEGF, iNOS, MMP-9, TNF-α, CD14 and change in macrophage migration/invasion were assessed.

Results: The expression of key RAS components (AT1/AT2 receptors) by P338D1 cells were confirmed using immunofluorescence. AT1 receptor blockade decreased the expression of iNOS, MMP-9, VEGF and CD14 but increased TNF-α when compared to AT2 receptor blockade. Phalloidin staining showed higher filopodia and focal adhesion formation following AT1 receptor blockade compared to AT2 receptor blockade by macrophages. However, the migration assay using fibronectin coated transwells revealed no difference in migration.

Conclusions: Macrophages possess the ability to respond and produce RAS components. The RAS can alter the production of key growth factors important during tumour development by macrophages. This study confirms the counter-regulatory role of AT1/AT2 receptor activation.
EPITHELIAL TO MESENCHYMAL TRANSITION (EMT) A MECHANISM ADOPTED BY TUMOUR CELLS IN RESPONSE TO DRUG TREATMENT
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Background: More than one million people are diagnosed with colorectal cancer (CRC) each year and over half a million die annually, with liver metastasis being the predominant cause. Apart from a small group amenable to surgery, the majority of patients are treated with palliative chemotherapy. We have previously tested the effect of a vascular disruptive agent, Oxi4503 in a mouse model of colorectal liver metastases and have shown that it reduces the tumour mass by about 90%. However, a small population of cancer cells persists at the tumour periphery. The mechanisms by which these tumour cells evade treatment are poorly understood.

Method: We investigated changes in cell morphology and pro-angiogenic growth factors at various time points post Oxi4503 treatment.

Results: Tumour cells that survived the treatment were acutely hypoxic. Oxi4503 treatment induced significant upregulation of pro-angiogenic factors (HIF-1α, HGF, VEGF and TGF-β). Additionally we found rapid and widespread EMT following drug treatment. It involved all surviving tumour cells; characterized by significant down regulation of E-cadherin, marked upregulation of mesenchymal markers ZEB1 and Vimentin, redistribution of β-catenin from the cell junctions to cytoplasm and nucleus. Our study is the first, to our knowledge, to demonstrate in vivo EMT that involves essentially all surviving tumour cells following treatment. In preliminary results we observed similar EMT in other cancer treatment modalities including cytotoxic and anti-angiogenic therapies. These findings indicate that EMT may represent a common survival mechanism adopted by stressed tumour cells and as such may have significant clinical implications in cancer therapy.

HYPERTENSION IN ABDOMINAL AORTIC ANEURYSMS – A RATIONAL TARGET FOR CHRONOTHERAPY?
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2Department of Vascular Surgery, Austin Health, Heidelberg, VIC, Australia

Introduction & aims: Clinic measurements of blood pressure (BP) only poorly predict development of abdominal aortic aneurysm (AAA). Nevertheless, rupture of AAA follows a diurnal pattern with most ruptures occurring in the morning. We hypothesised that the inability of clinic measurement to predict AAA could be explained by an abnormal diurnal variation of BP.

Methods: We retrospectively compared ambulatory BP records of patients with AAA attending our Blood Pressure Clinic over a 5 year period with sex and age matched controls. We then performed a prospective study of patients scheduled for elective AAA surgery attending the Vascular Clinic. In addition to a medical assessment, we also measured 24 hour ambulatory BP, postural BP and diurnal urine output.

Results: In the retrospective study, only 2 of 27 patients with AAA had normal diurnal BP variation, compared to 16 of 27 control patients (p<0.001). The mean night systolic BP was significantly higher in AAA vs controls (137.7±3.4 mmHg vs 124.4±3.1 mmHg). In the prospective study (n=37), 30 % patients had a normal blood pressure variation, 52 % had postural hypotension and 72% had nocturnal polyuria.

Conclusion: AAA is associated with a high prevalence of abnormal BP variation, postural hypotension and nocturnal polyuria. Ambulatory blood pressure monitoring should be included in the assessment of patients with AAA to detect hidden nocturnal hypertension, which is a potential therapeutic target and further studies are needed to assess the effect of treatment of this on AAA progress and outcome.
MORPHOLOGICAL STUDY OF INFILTRATING CELLS FOLLOWING SEVERE ACUTE CELLULAR REJECTION OF RAT LIVER ALLOGRAFT - IMPACT OF HYPERBARIC OXYGEN THERAPY

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Introduction: Acute cellular rejection is a common cause of post transplantation morbidity. Hyperbaric oxygen therapy (HBO) has been shown to impact ischemia reperfusion injury. However its safety and efficacy has not been conclusively studied in a rejection model of liver transplantation.

Methods: Male inbred Dark Agouti and Lewis rats were transplanted to create severe acute cellular rejection. HBO was administered twice daily for one, three, and seven days following transplantation after which liver tissue was collected for histopathology. Kupffer cell infiltration was observed via immunohistochemistry for ED2 antigen respectively. Neutrophil infiltration was observed via naphthol AS-D chloroacetate esterase staining.

Results: Overall there was no significant effect in Kupffer cells and total infiltrating cells. However there was a trend for increasing Kupffer cell numbers following treatment in the periportal (Zone 1) region, perivenous (Zone 3) region (p=0.003) and the area between (Zone 2) (p=0.001). There was also a trend to increase percentage of Kupffer cells although this was not statistically significant in all Zones at all timepoints. An increase in the number of neutrophils was seen at Day 1 following treatment in both Zone 1 (p=0.041) and 3 (p=0.046). However there was no significant effect at other timepoints.

Conclusions: HBO therapy was seen to have a varied impact on the infiltrating T cells, Kupffer cells and neutrophils. Further studies are required to clearly elucidate its mechanisms of action.

VALVE-SPARING AORTIC ROOT REPLACEMENT AND AORTIC VALVE REPAIR: A 10 YEAR SINGLE-CENTRE EXPERIENCE.

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Objective: Preservation of the native aortic valve in aortic root replacement avoids anticoagulation and potentially offers greater durability than a bio-prosthesis. We reviewed our experience with these techniques and in particular, the durability of additional leaflet prolapse repair in stretched leaflets.

Methods: From 1999 to 2010, 95 patients underwent valve sparing aortic root replacement of which 69 (73%) had leaflet prolapse requiring correction. There were 66 (69%) males while mean age was 58 ± 14 years. Seventy-nine (83%) patients had tricuspid valves. Grade 3+ or 4+ aortic regurgitation (AR) was present in 61 (64%) patients. Acute aortic dissection occurred in 5 patients. The re-implantation technique was performed in 87 (92%) and the remodeling in 8 (8%). Concomitant procedures were performed in 35 (37%) cases including aortic arch reconstruction in 19 (20%).

Results: There were 4 (4.2%) in-hospital and 6 late deaths. Mean follow up was 34 ± 29 months and was 98% complete. At 6 years, survival was 86% ± 5.1% while freedom from >2+ AR was 88% ± 4.5% in the entire cohort and 93 ± 3.2% in those with tricuspid valves. Overall freedom from aortic valve replacement was 87% ± 6.6%. Patients who had leaflet prolapse correction experienced similar valve repair durability compared to those who did not require it (85 ± 6.2% vs. 95 ± 4.6%, p=0.36).

Conclusion: Valve-sparing aortic root replacement with added aortic valve repair leads to good durability. This has allowed valve preservation in a sizable sub-group who would otherwise have received prosthetic valves.
BRANCH-FIRST AORTIC ARCH REPLACEMENT WITH NO CIRCULATORY ARREST OR DEEP HYPOTHERMIA.

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²Department of Anaesthesia, Austin Hospital, Melbourne, VIC, Australia

Background: For aortic arch surgery, the risks of deep hypothermic circulatory arrest with or without antegrade cerebral perfusion have been well documented. We hereby describe our early experience with a "branch-first continuous perfusion" technique which by avoiding deep hypothermia and circulatory arrest, may potentially reduce morbidity and mortality.

Methods: Arterial perfusion is peripheral using femoral, axillary and graft side-arm inflows. Disconnection of each arch branch, and anastomosis to the trifurcation graft, proceeds sequentially from the innominate to the left subclavian artery, with continuous perfusion of the heart and viscera by lower body and brain by upper body arterial return. After clamping the descending aorta, the debranched arch may then be replaced and connected to the ascending aorta before the common stem of the trifurcation graft is joined to the arch graft. Thirty-six patients underwent this technique. Fifteen patients (42%) were operated for aortic dissection, and the remainder for aneurysms.

Results: With experience, minimum pump temperature rose from 16 to 34 degrees. There was 1 (2.8%) mortality, while 2 (5.6%) patients experienced neurological dysfunction. Extubation was achieved within 24 hours in 16 (44%) patients while 17 (47%) left ICU within 2 days. Twelve (33%) patients were discharged from hospital within 7 days. Eight (22%) patients required no transfusion of blood.

Conclusions: This technique brings us closer to the goal of arch surgery without cerebral or visceral circulatory arrest and the morbidity of deep hypothermia. Early results are encouraging. Greater numbers and follow-up will reveal the full potential of this approach.
Some authors have provided pdfs of their posters these are included here.
BACKGROUND

Liver transplant has become the treatment of choice for a variety of acute and chronic liver diseases, as well as liver cancers. Internationally, liver transplant units are large, specialist facilities. Australia has established five state based services for liver transplants, spread across the country to minimize distance and travel time for treatment. The Victorian Liver Transplant Unit (VLTU) includes Austin Health and the Royal Children’s Hospital. Austin Health is the adult liver transplant provider for Victoria, Tasmania and Southern New South Wales, performing approximately 50 transplants per year.

VLTU and OT

Austin Health have provided part-time OT for > 10 yrs.

Provide interventions along the continuum of care - both pre and post transplant and across inpatient and outpatient settings

Client centered interventions may include
- home assessment,
- equipment prescription,
- energy conservation,
- stress management,
- provision of information and education for liver disease symptom management
- advice on graded return to work & leisure occupations, return to driving
- delivery of group education sessions.

LITERATURE REVIEW

- Extensive literature search conducted – 32 keywords across 11 databases.
- Over 350 articles identified as potentially relevant to occupational therapy and the field of liver transplantation.
- Annotated bibliographies developed around diverse themes such as driving, return to work, encephalopathy, energy conservation and patient experience.
- Only 3 of the articles directly linked or discussed occupational therapy and liver disease or transplantation.
- Elliott & Newton (2009) advocate for OTs to better understand the experiences that shape a person’s ability to function with liver disease.
- Elliott et al (2010) highlight that OTs have a major role in addressing the symptoms associated with liver disease but the available evidence to support this is lacking.
- Hastings et al (2004) provide preliminary evidence for the effectiveness of OT to improve the function of individuals who have had an organ transplant.

REFERENCES


FUTURE PLANS

Informing the OT profession, and the transplantation field more broadly, of the emerging area of practice of OT for liver transplant patients, via conference presentations and journal articles.

Developing a community of practice with OTs working in other solid organ transplant multidisciplinary teams.
WHAT CALCULATIONS DID OUR INSULIN PUMP PATIENTS START OUT ON?

Roberts, L. Stevenson, V. Diabetes Education Services, Austin Health, Heidelberg, Victoria

Background:
The Diabetes Educators (DE) at a metropolitan teaching hospital were interested in reviewing the continuous subcutaneous insulin infusion (CSII) start rates of patients using standard existing protocols1,2 (Figure 1). This would provide the Diabetes Department with more in-depth information about our new CSII patients.

Aim: To profile patients start up pump calculations.

Method:
Data was analysed mainly from post pump initiation clinic letters (Figure 2). These letters were sent to the referring Endocrinologist from the DE. This followed routine admission to the Ambulatory Care Unit or paediatric ward for all CSII patients. Education included relevant pump education and establishing CSII commencement rates and other settings. Patients were all seen by the endocrine or paediatric registrar for admission, the DE for education and all had previously a dietitian to learn carbohydrate counting. All 27 patients commenced on one background basal insulin rate, all used the same brand meter and were given advice for blood glucose testing i.e. pre meal, 2 hour post meal testing, 2200, 2400 and 0300. Insulin action time was set and target BGL's were agreed upon. The management of hypoglycaemia and hyperglycaemia and the significance of positive ketones were emphasised to all patients and their families. All had telephone contact availability with the DE, endocrine or paediatric registrars being available after hours.

Results:
Data was compiled from July 2008 to April 2010 for 27 patients with type 1 diabetes who were commencing CSII for the first time. The characteristics and CSII commencement rates of the study cohort are shown below which represents age, duration of diabetes, anthropometrics, basal, bolus rates and insulin sensitivity factor (ISF) (Tables 1 & 2). CSII upgrade patients were excluded in this study. The eleven children were of similar age, height, weight and had similar mean insulin to carbohydrate bolus ratios. Composite images of the height and weight of paediatric males and females are as shown (Figure 3). In respect to the duration of their diabetes, paediatric females commenced CSII earlier with lower beginning basal rates than paediatric males. Sixteen adults were of similar age and mostly overweight. A composite image of the adults BMI of 29.8 and 26.06 are shown respectively (Figure 4). In respect to the duration of their diabetes, adult females commenced CSII earlier with a slightly higher basal rate than adult males. Interestingly, paediatric males had similar mean basal rates when compared with adult males. Paediatric females required approximately 50% less basal insulin rates than that of adult females. Compared with adults, children required approximately half of the amount of insulin to carbohydrate bolus ratios. In respect to the ISF, children appear to have been more sensitive to insulin than adults.

<table>
<thead>
<tr>
<th>Total 11 100%</th>
<th>*Age (yrs)</th>
<th>*Yrs of DM</th>
<th>*Ht (cm)</th>
<th>*Wt (kg)</th>
<th>*Basal (units/hr)</th>
<th>*Bolus (1:CHO g)</th>
<th>*ISF (1unit:mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (n=7)</td>
<td>10±3.76</td>
<td>2.0(4.6-6)</td>
<td>146</td>
<td>39</td>
<td>0.56(0.35-0.85)</td>
<td>1.20(3.13-29)</td>
<td>1.4(2.5-5.4)</td>
</tr>
<tr>
<td>M (n=4)</td>
<td>11±4.90</td>
<td>7(2-10)</td>
<td>150</td>
<td>45</td>
<td>0.83(0.2-1.3)</td>
<td>1.22(3.8-58)</td>
<td>1.4(1.2-13)</td>
</tr>
</tbody>
</table>

Table 1. Paediatric CSII patient data

<table>
<thead>
<tr>
<th>Total 16 100%</th>
<th>*Age (yrs)</th>
<th>*Yrs of DM</th>
<th>*BMI (kg/m2)</th>
<th>*Basal (units/hr)</th>
<th>*Bolus (1:CHO g)</th>
<th>*ISF (1unit:mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (n=6)</td>
<td>41.16±14.85</td>
<td>13.7(5-37)</td>
<td>29.8±8.88</td>
<td>1.05(0.6-2.15)</td>
<td>1.11(6.5-17)</td>
<td>1.22(1.2-6)</td>
</tr>
<tr>
<td>M (n=10)</td>
<td>39.7±15.36</td>
<td>19.3(2-45)</td>
<td>26.02±3.24</td>
<td>0.93(0.4-2.0)</td>
<td>1.12(5.24)</td>
<td>1.26(2-4.8)</td>
</tr>
</tbody>
</table>

Table 2. Adult CSII patient data

* = Mean

Conclusion:
In conclusion, this project summary has provided the hospital's Diabetes Department with a useful profile of how beginner CSII adults and children started out. The reasons why children commence pumps earlier than adults needs further exploration.

References:
Introduction/Background:
A diabetes service has been initiated within an outpatient mental health service at Austin Health. People with a mental illness have many additional risk factors for the development of type 2 diabetes but are unlikely to access the Diabetes Complications and Assessment Service (DCAS) run by Austin Health and our partner Community Health Services (CHS). In view of the heightened risks, people with a mental illness fall within the target groups for the Health Independence Programs, including the Hospital Admission Risk Program (HARP).

Methods:
Meetings were held between psychiatry and the Austin HARP diabetes program to gauge feasibility of such a service and the program was funded for a pilot period of 6 months commencing January 2011. A Credentialed Diabetes Educator (CDE) who is also a psychiatric nurse will attend the mental health clinic for 6 hours weekly. She will initiate a database of all patients and ensure the correct diabetes pathology tests are completed. The CDE will respond to abnormal results in consultation with the patient, psychiatrist, case manager and GP. Collaboration will improve the ability of mental health staff to manage diabetes. It is hoped that the CDE can form an initial rapport with the patient by commencing diabetes education at the mental health clinic and then encourage the patient to return for an annual assessment at the DCAS clinic. This will ensure the patient sees an endocrinologist, podiatrist and dietician. The clinic is bulk billed and the same CDE works across both mental health and DCAS sites, ensuring continuity for the client. Quality of care is enhanced by the electronic patient record system which is accessible both teams from any location.

Results:
The service has only been running for 8 weeks so results are unavailable. However, the database shows the mental health clinic has 260 clients of whom approximately 50% have completed diabetes screening in the past 6 months. Steps have been taken to improve pathology testing in the inpatient unit, the Clozapine Clinic and to increase awareness of outpatient medical staff.

Conclusion:
Diabetes at Mental Health is in its infancy. So far the database has revealed the gaps in diabetes screening for this high risk group. Review of medical histories of clients with known diabetes has show poor attendance for endocrine review appointments. These clients have been offered initial follow up at Diabetes at Mental Health. Some clients with diabetes are being well managed through shared care with their GP. It is hoped that this flexible, collaborative approach will result in improved diabetes management for people with a mental illness.