Letter from the Executive Director of Research

Research Week is one of the highlights of the Melbourne Health calendar. It provides a focus on research where all members of our staff and the community can reflect on the value of research and celebrate the advances in medical science.

The week-long program includes an address in the Opening Session by clinician and researcher, Professor Kate Leslie who is the Head of Research in the Department of Anaesthesia and Pain Management. Activities continue with a formal symposium, plenary talks, and interactive research education. Light relief comes in the form of the annual Great Debate. We continue to inform visitors to the hospital with a community engagement booth in the hospital foyer.

I would like to thank the Research Week Committee who managed to pull together a wonderful program.

Thank you to –
  Dr Giovanna D’Abaco
  Ms Carol Jewell
  Ms Catherine Lander
  Professor Danny Liew
  Ms Angela Magira
  Professor Terry O’Brien
  Dr Angela Watt

In addition, the efforts of those involved in selecting the suitable abstracts and in the adjudication of the Awards and those coordinating and chairing sessions during Research Week are greatly appreciated. Melbourne Health Research Week is successful because of the generous contributions of time, energy and expertise by so many people – thank you.

Professor Ingrid Winship
Executive Director Research
DAY 1 - THURSDAY 23 MAY 2013

Opening Session

1.00 – 2.00 pm, Charles La Trobe Lecture Theatre, Function and Convention Centre, Ground Floor, RMH (Lunch at 12.30 pm)

Welcome address: Professor Ingrid Winship, Executive Director of Research, Melbourne Health

Key Note Lecture: Professor Kate Leslie, Head of Research, Department of Anaesthesia and Pain Management, “Multi-centre perioperative clinical trials”

Plenary Presentation: 1 - Dr Bruce Campbell, “Predicting hemorrhage after thrombolysis using advanced imaging”

DAY 2 – FRIDAY 24 MAY 2013

Research Symposium

Concurrent Sessions: 9.15 – 10.15 am, Seminars Room 1 & 2, Function and Convention Centre, Ground Floor (Morning Tea at 10.15 am)

Session 1, Seminar Room 1

2 Zhen Zeng, Characterization of the electrophysiological properties of Nav1.1 and Nav1.2 expressed in HEK293T cell lines
3 Rejhan Idrizi, Investigating the role of betacellulin in the plasma of schizophrenia patients treated with the antipsychotic clozapine
4 Nadia Warner, The dual selection and persistence of an immune escape, drug-resistant, defective HBV strain
5 Ping Zheng, Sodium selenate reduces neurodegeneration and behavioural impairments in the post-kainic acid status epilepticus rat model of temporal lobe epilepsy

Session 2, Seminar Room 2

6 Scott Wilson, A novel method to profile the cardiovascular stability of dialysis patients by continuous measurement using a median hybrid preprocessing filter algorithm
7 Jonathan Goh, Review of optic nerve sheath fenestrations: indications and outcomes
8 Sangeetha Ramdave, Association between CYP2C19 variants and efficacy of Clopidogrel in patients after neurointerventional procedures
9 Michael Wong, Characterisation of catheter-tissue contact force during epicardial RF ablation in an ovine model

Session 3, Seminar Room 1

10 Sarah Hanieh, The effect of intermittent antenatal iron supplementation on infant outcomes in rural Vietnam: a cluster randomised trial
11 Jacqueline Osborne, Investigating practices relating to malnutrition in Victorian cancer services: results from the point prevalence study
12 Natalie Marijanovic, Identifying risk factors for hypoglycaemic episodes in hospital inpatients
13 Sheena Sullivan, Evidence not shown for waning of influenza vaccine effectiveness during the 2012 influenza season in Victoria, Australia

Session 4, Seminar Room 2

14 Louise Weir, Direct-to-CT model halved RMH stroke thrombolysis door-to-needle times to 25 minutes in just four months
15 Vilija Jokubaitis, Predictors of 12-month confirmed disability progression after onset of clinically isolated syndrome (CIS) suggestive of multiple sclerosis
16 Tomas Kalincik, Relapse incidence in women and men throughout the course of multiple sclerosis: an MSBase cohort study
17 Aleisha Gorski, Impact of an emergency general surgical service on time to theatre
Poster Viewing Session

11.45 am – 12.45 pm, Function and Convention Centre, Ground Floor, RMH
(Lunch at 12.00 pm)

Melbourne Health Research Week 2013 will display over 130 posters showcasing research in many fields including Infectious Disease, Cancer, Immunology, Nephrology, Cardio-respiratory, Neurosciences, Aged Care, Mental Health, Youth Health, Anaesthesia and Pain Management, Surgery, Emergency, Genetics, Endocrinology, Quality of Care and Medical Imaging. Presenters will be on-hand to discuss their projects.

The Great Debate

1:00 – 2:00 pm, Charles La Trobe Lecture Theatre, Function and Convention Centre, Ground Floor, RMH
(Lunch at 12.00 pm)

“Happy 165th birthday, RMH! You've come a long way...for the better or for worse?”

The Royal Melbourne Hospital turned 165 this year but should we be celebrating? Are things better in 2013 compared with the time of the new Melbourne Hospital in 1848? Or could we spare more time with our patients then?

Melbourne Health has called together some of the greatest minds of our eminent institution to use their collective intellect to tackle this most challenging issue in the form of a Great Debate.

Master of Ceremonies (MC)
› Professor Ingrid Winship, Executive Director of Research

The proceedings will be presided over by a panel of distinguished judges:
› Dr Gareth Goodier, Chief Executive
› Ms Christine Fitzerbert, Executive Director of Human Resources
› Ms Sharon McGowan, Executive Director Communications and Community Relations
› Mr Colin Holland, Executive Director, Finance and Logistics

Team for the Affirmative – “Team – For the better”
› A/Professor Peter Morley, Director of Medical Education
› Ms Sally Campbell, Executive Director Corporate and Information Services
› Professor Louis Irving, Head Respiratory and Sleep Disorders Medicine

Team for the Negative – “Team – For the worse”
› A/Professor Genie Pedagogos, Consultant Nephrologist
› Dr Dan Steinfort, Respiratory Physician
› Dr Sam Hume, Director of Physician Education and ID Physician
Surgical Research Forum
8.30 – 9.30 am, Ewing Lecture Theatre, Level 5, Clinical Sciences Building

Chaired by Professor Andrew Kaye

18 Rose Shakerian, Does consultant-led care within an acute care surgical unit improve patient outcomes at a level 1 trauma centre?

19 Andrew Nichols, DTI tractography reveals changes in the optic radiations of patients with persistent visual impairment following surgery for optic chiasm compression

20 Chunyan Ma, The role of TGF-β-Smad1/5 signalling in tumour cell endothelialisation

21 Wayne Ng, Murine Orthotopic Bioluminescent Glioma Stem Cell Xenograft Model

22 Jingyi Sheng, TGF-β and autoimmune diseases in human and mice

23 Stanley Styli, The Tks5 adaptor protein – a regulator of invadopodium function and metastasis in cancer cells

How to Undertake Small Clinical Studies Pt. 1
19.00 am – 12.00 pm, 7 East Seminar Room, Main Building, RMH

Study designs and basic epidemiological and statistical concepts

This session is coordinated by the Melbourne EpiCentre. Registration is required for this session as there are limited places. To register, please send an email to: Wendy.Lemaire@mh.org.au or telephone 9342 8772.

How to Undertake Small Clinical Studies Pt. 2
9.00 am – 12.00 pm, I.T. Training Room, Basement, Main Building, RMH

Data analysis using Microsoft Excel

This session is coordinated by the Melbourne EpiCentre. Registration is required for this session as there are limited places. To register, please send an email to: Wendy.Lemaire@mh.org.au or telephone 9342 8772.
DAY 6 – WEDNESDAY 29 MAY 2013

Allied Health Research Skills

1pm - 3.00 pm, Seminar Room 1, Function and Convention Centre, Ground Floor, RMH

Research Skills Workshop

The aim of this informal interactive workshop, chaired by Professor Danny Liew, is to guide allied health clinicians who want to build research into their everyday practice. Two case studies will be presented to illustrate how to go about gaining approval for quality assurance applications and formal ethics/research governance applications. A panel of experienced researchers will also share their wisdom and experience on the topic.

3.15pm – 4.30pm, Seminar Room 1, Function and Convention Centre, Ground Floor, RMH

Research Symposium

The workshop will be followed by a short symposium consisting of three presentations illustrating different approaches to developing and progressing clinical relevant research. This will include a brief background of their research, their progress to date and the lessons they have learnt in the process.

DAY 7 – THURSDAY 30 MAY 2013

RMH Academic Research Centre Symposium

Genomics Advancing Translational Research

9.00 am – 12.30 pm, Charles La Trobe Lecture Theatre, Function and Convention Centre (Lunch at 12.30 pm)

Chair: Professor Patricia Desmond
Opening Address: Professor James Angus
Key Note Lecture: Dr Gareth Goodier,
What it means to be a world leading academic medical centre in the 21st century

The opening of the RMH Academic Research Centre Symposium 2013 is followed by a series of presentations from experts in various disciplines with research using genetics in Medicine, Radiology, Obstetrics and Gynaecology, Surgery, and Psychiatry.

Closing Ceremony

1.00 – 2.00 pm, Charles La Trobe Lecture Theatre, Function and Convention Centre (Lunch at 12.30 pm)

Chair: Professor Ingrid Winship
Plenaries:
Dr Julianne Bayliss
Hepatitis B splicing is enhanced prior to development of hepatocellular carcinoma

Dr Mary Ann Anderson
Specific inhibition of Bel-2 by ABT-199 as treatment for Chronic Lymphocytic Leukemia

Final presentations for Research Week followed by the annual awarding of the Research Week prizes handed out by the Executive Officer of Melbourne Health, Dr Gareth Goodier. Prizes will be awarded for best oral and poster presentations as well as the winner of this year’s Cleveland Young Investigator Award.
1 DR BRUCE CAMPBELL

PREDICTING HEMORRHAGE AFTER THROMBOLYSIS USING ADVANCED IMAGING

CAMPBELL BCV, Christensen S, Straka M, Mlynash M, Sharma G, Parsons MW, Bammer R, Marks MP, Lansberg MG, Albers GW, Donnan GA, Davis SM.
Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Australia
Stanford Stroke Center, Stanford University, Stanford, California

Background and purpose: Hemorrhagic transformation is the major complication of reperfusion therapies and carries a high risk of disability and death. Very low cerebral blood volume (VLCBV) and increased blood brain barrier permeability, both markers of severe ischemia, have been proposed as imaging predictors of hemorrhage risk. We aimed to compare the prognostic power of these two approaches using data from the DEFUSE 2 study.

Methods: Acute ischemic stroke patients had perfusion-diffusion MRI before and within 12 hr after endovascular therapy. Baseline cerebral blood volume (CBV) maps were generated and the volume of VLCBV (CBV<2.5th percentile of the normal hemisphere) was calculated. Permeability was assessed using two recirculation parameters: “relative recirculation” (rR): the difference in area encompassed by the observed tissue-concentration curve and a theoretical fit of the first pass bolus; and percent recovery (%Recovery): the difference in signal intensity between peak bolus and average post-bolus. Parenchymal hematoma (PH) was defined as intracerebral blood clot with mass effect. The more clinically relevant subset of type 2 PH (PH2) occupying >30% of the infarcted tissue was also examined. Reperfusion was defined as >50% reduction in Tmax>6sec lesion volume between baseline and post-procedure MRI. Logistic regression models were compared using Bayesian Information Criterion (BIC).

Results: In DEFUSE 2, MRI prior to catheter angiography was performed in 110 patients, 59 had tPA pre-treatment and 25 developed PH, including 11 PH2. In 100 patients with technically adequate acute perfusion MR, preliminary receiver operating characteristic analysis identified >40%rR and <50%Rec as the optimal thresholds to assess the volume of tissue with increased permeability. In logistic regression, PH was associated with increased VLCBV (p=0.01) and %Recovery permeability (p=0.03) but not rR (p=0.10). The VLCBV model had better fit than %Recovery permeability (BIC difference +1.9). The more severe PH2 were associated with VLCBV (p=0.03) but not %Recovery (p=0.31) or rR (p=0.13). The VLCBV model for PH2 had better fit than %Recovery (BIC difference +4.3) or rR (BIC difference +3.2) permeability. VLCBV remained associated with PH2 (p=0.03) after adjustment for the key prognostic factors of baseline stroke severity and age.

Conclusions: VLCBV was a stronger predictor of early PH after reperfusion than permeability parameters in patients treated with endovascular therapy. This adds to our previous work on VLCBV and hemorrhage risk after intravenous tPA. Further work to develop automated calculation of VLCBV with prospective validation is planned.

2 MR ZHEN ZENG

CHARACTERIZATION OF THE ELECTROPHYSIOLOGICAL PROPERTIES OF NAV1.1 AND NAV1.2 EXPRESSED IN HEK293T CELL LINES

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The University of Melbourne, The Royal Melbourne Hospital

Purpose: Nav1.1 and Nav1.2 are two main voltage-gated sodium channel subtypes expressed predominantly in central neurons. While their distributions in the central nervous system may be different, their existence is absolutely vital. The malfunction of these channel subtypes can also result in conditions with a range of severity. Voltage-gated sodium channels can be activated before entering a non-conducting inactivated state. They are the molecular target of many therapeutic agents including anti-epileptic drugs and local anaesthetics. The understanding of the differences of the mechanism of action of these two Nav subtypes is implicated in various roles they played during disease manifestation, drug modulation as well as normal neuronal functioning.

Methods: Voltage clamp was done on HEK293T cell lines expressed with human Nav1.1 and Nav1.2 alpha subunits. Sodium currents in the whole cell configuration were recorded. Activation and inactivation properties were investigated. In addition, resting and dynamic situation of the channels corresponding to the resting and stimulated excitable cells were examined with various protocols.

Results: n=61. Steady state inactivation parameters were measured with 50, 500 and 1000 ms conditioning pulses (CP’s). Interestingly, increasing duration of CP’s resulted in a negative shift in the hinf curves, which appeared the same for both channel types (V0.5(50) –63.8±2.7, –64.6±1.6, V0.5(500) –70.8±2.6, –74.1±2.0, V0.5 (10000) –75.5±3.2, -78.9±3.0 for Nav 1.1 and 1.2 respectively). The proportion of channels transferred to inactivated states with longer pulses was quite different between the channels subtypes.(Nav 1.1, n=11; Nav 1.2, n=9). Nav 1.1 had about 40% less
channels (n=7) inactivated with transitions from -70 to -100 mV and more Nav 1.2 channels entered inactivation with potentials changes from -100 to -60, -70, and -80 mV (n=25). Nav 1.1 was less affected by use-dependent inactivation elicited by 40 Hz depolarization (n=6). Additionally, Nav 1.1 had a smaller proportion of channels were transferred to the slow inactivated state with 10 s pulses compared with Nav 1.2. Conclusion: Nav 1.1 channels are less affected by slow inactivation processes and use dependent inactivation than Nav1.2. These differences may account for the high frequency firing behavior seen in the majority of interneurons which are known to have a predominance of Nav 1.1 subtype. It will be of great interest to see the effect drugs such as lacosamide that seem to target slow inactivation processes in Nav channels.

3 DR REJHAN IDRIZI

INVESTIGATING THE ROLE OF BETACELLULIN IN THE PLASMA OF SCHIZOPHRENIA PATIENTS TREATED WITH THE ANTIPSYCHOTIC CLOZAPINE

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Department of Psychiatry, Northern Psychiatry Research Centre, the Northern Hospital, Cooper Street, Epping 3067, Victoria Australia
Background: Schizophrenia is a complex neuropsychiatric disorder of unknown aetiology however recent studies have implicated epidermal growth factor (EGF)/ErbB-system dysfunction. Betacellulin (BTC) is an EGF family ligand for ErbB1 and ErbB4 receptors and has been demonstrated to be elevated in the serum of schizophrenia patients. Furthermore our previous in-vitro, in-vivo and clinical data support clozapine’s augmentation of deficient ErbB1 signalling suggesting a mechanism for its therapeutic efficacy. We therefore postulated that BTC levels are altered in schizophrenia and that they may be influenced by clozapine treatment.

Objectives: In this study we sought to prospectively evaluate plasma BTC levels in a clozapine-treated schizophrenia cohort over a 26-week treatment period and in healthy control subjects.

Methods: We used an ELISA assay to measure plasma concentrations of BTC in schizophrenia patients prior to (n=39), 2-weeks (n=22), 6-weeks (n=21) and 26-weeks (n=38) after clozapine treatment and also in age/gender matched healthy controls. The Positive and Negative Syndrome Scale (PANSS) and CGI were administered at baseline, 6 and 26 weeks of treatment.

Results: Mean BTC levels were significantly lower in patients at baseline (2280±3496pg/ml, mean±SD), 2-weeks (1782±2749), 6-weeks (1938±2939) and 26-weeks (2195±3938) compared to controls (2536±1585). Post-treatment BTC levels at 26-weeks significantly correlated with PANSS positive score (r²=0.176; P<0.05; N=35) and with PANSS change % (r²=0.143; P<0.05; N=38). Furthermore at 26-weeks there was a significant difference in BTC levels between responders (n=19) (symptom improvement of ≥20%) and non-responders (n=19; P=0.034).

Conclusions: Schizophrenia patients on antipsychotic drugs have significantly lower BTC levels compared to healthy controls. It would appear that the lower the BTC value the greater the treatment response in particular with reference to positive symptoms. This suggests that BTC activation of ErbB1 and/or ErbB4 may adversely impact on treatment response. Given our previous clozapine findings, we hypothesise that adverse BTC effects may be principally mediated through ErbB4.

4 DR NADIA WARNER

THE DUAL SELECTION AND PERSISTENCE OF AN IMMUNE ESCAPE, DRUG-RESISTANT, DEFECTIVE HBV STRAIN

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INTRODUCTION: The hepatitis b virus (HBV) surface gene overlaps completely with the polymerase/reverse transcriptase (rt) gene, hence one nucleotide change can alter both proteins. Polymerase mutations generally confer drug resistance, whereas surface mutations confer immune escape. rtA181T/sw172* is a strain that confers drug resistance due to rtA181T change, and a stop codon at position 172 in the overlapping surface. This variant is defective in secretion and promotes apoptosis.

The accepted view is that this virus becomes the predominant quasispecies due to its drug-resistance, and that the stop codon in the surface is secondary to this change. However, there are several SNPs that encode rtA181T, which do not cause a surface stop codon. Despite this, rtA181T/sw172* is consistently selected at a high rate, suggesting that there may be another selection pressure involved. The region of the HBsAg that is lost due to sw172* contains a major CTL epitope of HBsAg (aa172-180) leading to the hypothesis that rtA181T/sw172* is also an ‘immune escape’ variant providing the virus with a selective advantage due to evasion of the CTL response.
METHODS: We analysed matched cohorts of HBV-infected, drug naïve, pregnant patients who had well-defined post-partum ALT flares, and a matched cohort who did not have ALT flares. ALT flares were used as an indication of a strong anti-HBV immune response. Serum samples were taken prior to and during ALT flare. An ultradeep SNP detection assay was developed using pyromark technology and used to detect the percentage of genomes encoding sW172* and sW182* (stop codon that does not cause loss of this CTL epitope).

RESULTS: Comparison of the two timepoints (pre- and during flare) revealed that patients who flared had a significant increase in sW172*, whereas patients who did not flare had no change in sW172*. The level of sW182* did not change in either cohort. Furthermore, the percentage increase in sW172* correlated with the percentage increase in ALT. No such correlation was observed for sW182*.

DISCUSSION: These results show that sW172* is positively selected during an immune-mediated ALT flare whereas sW182* is not, suggesting that sW172* is selected as an ‘immune escape’ variant. The sW172* variant also encodes rTa181T, which is positively selected during NA therapy. This is the first study to demonstrate this double selection pressure with the positive outcomes of immune evasion and drug resistance balancing the negative outcomes of defective secretion and host cell apoptosis.

5 MR PING ZHENG

SODIUM SELENATE REDUCES NEURODEGENERATION AND BEHAVIOURAL IMPAIRMENTS IN THE POST-KAINIC ACID STATUS EPILEPTICUS RAT MODEL OF TEMPORAL LOBE EPILEPSY

ZHENG, P., Shultz, S.R., Wright, D., Johnston, L., Hovens, C., Jones, N., O’Brien, TJ
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Hyperphosphorylated tau has been implicated in the pathogenesis of a variety of neurodegenerative disorders, including epilepsy. Here we investigated whether treatment with sodium selenate, a drug that reduces the pathological hyperphosphorylation of tau by increasing PP2A activity, would reduce neurodegeneration and functional impairments in a rat model of mesial temporal lobe epilepsy (mTLE). After four hours of status epilepticus induced by systemic kainic acid injections, or control-saline injections, young-adult male Wistar rats (n=9/group) were given continuous sodium selenate treatment (1 mg/kg/day), administered via subcutaneous osmotic mini-pump, for two months. In-vivo imaging with T2-weighted MR, diffusion weighted imaging, diffusion tensor imaging and magnetic resonance spectroscopy were used to assess structural and metabolism damage one month post-injury. Cognitive, motor, and emotional impairments were also assessed at one month post-injury. Video-EEG recording was used to evaluate the seizure frequency and duration. Immunohistochemical and western-blot analyses were used to assess levels of hyperphosphorylated tau and related pathologies. The results demonstrated that sodium selenate treatment reduced markers for neurodegeneration and behavioural impairments after a post-SE excitotoxic injury in the rat.

6 DR SCOTT WILSON

A NOVEL METHOD TO PROFILE THE CARDIOVASCULAR STABILITY OF DIALYSIS PATIENTS BY CONTINUOUS MEASUREMENT USING A MEDIAN HYBRID PREPROCESSING FILTER ALGORITHM

WILSON S, Becker G, Harrap S
Department of Nephrology, Royal Melbourne Hospital; University of Melbourne, Parkville

The detection of clinically significant haemodynamic instability is a challenge during haemodialysis (HD). Whilst the profile of a ‘normal’ blood-pressure (BP) response to HD is not described, continuous monitoring implies complex patterns and trends that are missed by standard intermittent arm-cuff measurement. The sensitivity of research-grade measurement devices when applied in the clinical setting creates a signal degraded by outliers, artifact and noise, a common obstacle in real-time physiological analysis. The ideal solution would involve signal preprocessing to yield an uncontaminated dynamic regression series reflecting the underlying BP profile.

Method: A continuous beat-to-beat BP dataset from the intradialytic period was captured in 10 established HD outpatients undergoing routine ‘short-break’ HD. Simulations using progressively complex moving-average, control-chart substitution and median-hybrid (MHF) filtering techniques were applied to determine the most robust technique to extract an accurate, analyzable series. Outputs were compared to the parent signal and validated using Bland-Altman analysis against a simultaneously collected independent brachial-cuff BP dataset from each patient.

Validation of signal integrity was performed using white-noise analysis by Fisher’s Kappa and Bartlett’s Kolmogorov-Smirnov methods.

Results: Continuous BP record from a standard HD yields in excess of 16,000 separate datapoints, mandating an automated approach. Solitary moving average filters perform well at white-noise exclusion but were susceptible to impulsive artifact and sustained measurement error where duration exceeded MA subset length. The intraindividual variation in optimal subset size saw no uniformly applicable metric. Control chart methods improve resistance to extreme outliers at the expense of poor white-noise attenuation and signal edge detection. Tighter arbitrary control limits reduced integrity of the output signal in an incremental fashion, eventually rendering a self-propagating loop of
uninterpretable data. The MHF output performed well to exclude outliers and create a single, analyzable time-series free of statistical white-noise (p<0.001). 46/50 (92%) time-coincident paired BP values met agreement limits, confirming the equivalence of the MHF output to the methods of standard clinical practice. In all ten patients, the absolute BP peaks and troughs revealed by continuous monitoring were not captured by arm-cuff observations. The intermittent brachial datapoints did not capture the magnitude, nor direction of smaller range net pressure changes over any time frame, or reliably identify directional changes in trend.

Conclusion: This paper represents the first design and application of MHF methodology to cardiovascular or clinical time-series data and will facilitate future analyses to characterize intradialytic BP behaviour, exploring associations between these with clinical and dialytic parameters.

7 Dr Jonathan Goh

REVIEW OF OPTIC NERVE SHEATH FENESTRATIONS: INDICATIONS AND OUTCOMES

Jonathan Goh, Thomas G Hardy

Purpose: To determine and compare the efficacy and safety of optic nerve sheath fenestration (ONSF) for idiopathic intracranial hypertension (IIH) and indications other than IIH from a major tertiary hospital and a specialty eye referral hospital in Australia from 2002 to 2012.

Method: All cases of ONSF were identified via Medical Benefits Scheme item numbers through medical records from 2002 to 2012. Histories were reviewed for indication of surgery, other treatments, complications, pre and postoperative outcomes including visual acuity, and visual fields were compared. All procedures were medial transconjunctival orbitotomy approaches disinserting the medial rectus muscle, and performed by a consultant or orbital fellow with direct supervision.

Results: Total of 39 patients (71 nerves). Indications included 28 cases of IIH, 3 cases of cerebral venous sinus thrombosis with papilloedema, 8 other causes. At day 30 ONSF for IIH had a high success rate (improved/stable) of 95%. ONSF for other causes had similar rates of 88% to 100%. Most complications were temporary: transient diplopia (n = 11, 28.2%), diplopia requiring surgery, ptosis, anisocoria, corneal dellen.

8 Ms Sangeetha Ramdave

ASSOCIATION BETWEEN CYP2C19 VARIANTS AND EFFICACY OF CLOPIDOGREL IN PATIENTS AFTER NEUROINTERVENTIONAL PROCEDURES

RAMDAVE S 1, Lin M 1, Zhu W 1, Singh S 1, Todaro M 1, 2, Mitchell PJ 3, Dowling RJ 3, Chan J 1, Yan B 1, 2, Kwan P 1, 2

1 Department of Medicine (RMH), The University of Melbourne, Parkville, VIC, Australia; 2 Department of Neurology, The Royal Melbourne Hospital, Parkville, VIC, Australia; 3 Department of Radiology, The Royal Melbourne Hospital, Parkville, VIC, Australia

Background: Clopidogrel is an antiplatelet therapy prescribed after neurointerventional procedures (e.g. coiling, intracranial arterial stenting) to prevent future cerebrovascular ischaemic events. Variants (*2 and *3) of CYP2C19, present in up to 15% of Caucasians, are associated with hypo-functioning of the encoded cytochrome P450 enzyme responsible for metabolising clopidogrel to its active form, which may lead to insufficient platelet inhibition. CYP2C19*17 is a hyper-metabolising allelic variant which may be associated with enhanced antiplatelet response to clopidogrel.

We aimed to determine whether these CYP2C19 variants are associated with platelet inhibition effects and clinical outcomes of clopidogrel treatment in patients who had undergone neurointerventional procedures.

Methods: Patients who received clopidogrel after neurointervention at the Royal Melbourne Hospital were recruited. Platelet inhibition effect of clopidogrel was measured by the Verify Now P2Y12 Assay and expressed as % P2Y12 receptor inhibition. Clinical outcomes (ischaemic or haemorrhagic events) at 3 months post-neurointervention were recorded. Blood samples were obtained for DNA extraction and CYP2C19 genotype (*1, *2, *3 or *17) was determined by PCR-RFLP. Platelet inhibition effect of clopidogrel and clinical outcomes were compared between patients with different CYP2C19 genotypes.

Results: 77 patients have been recruited (54 female, mean age 55.2 years ±10.5; 23 male, mean age 60.3 years ±11.0). 41 patients were genotyped for CYP2C19 variants and met clinical outcomes, 34 of which were also measured for platelet inhibition. CYP2C19*17 is a hyper-metabolising allelic variant which may be associated with enhanced antiplatelet response to clopidogrel.

Amongst those who were genotyped (n=41), 51.2% were homozygous carriers of CYP2C19*1, while at least one allele of *2 was carried by 24.3%, *3 by 2.4%, and *17 by 31.7%. Median (IQR) P2Y12 receptor inhibition was 37.5 % (14-71%) among the *1/*1(n=16) carriers, 37% (17-70%) for those with one or more hypofunctioning allele (*1/*2, *1/*3, *2/*2, *2/*3, or *3/*3; n=7), 30% (18-49.5%) among those with at least one hyperfunctioning allele (*1/*17 or *17/*17; n=9), and 74% (54-94%) among those with one hypofunctioning and one hyperfunctioning allele (*2/*17 or *3/*17; n=2). Out of the patients with at least one hyperfunctioning allele (n=10), two had an incidence of haemorrhage and three had ischaemic events; whilst one patient who expressed a hypofunctioning and
hyperfunctioning allele also had haemorrhage. Of the CYP2C19*1/*1 carriers (n=21), two experienced an ischaemic event, while three had an incidence of bleeding. No ischaemic or haemorrhagic events were experienced by the other genotype groups.

Conclusion: Detection of hypo and hyper-functioning CYP2C19 variants could be a possible predictor of clopidogrel efficacy and clinical outcomes in patients’ post-neurointervention.

**9 DR MICHAEL WONG**

CHARACTERISATION OF CATHETER-TISSUE CONTACT FORCE DURING EPICARDIAL RF ABLATION IN AN OVINE MODEL

Department of Cardiology, RMH; Department of Veterinary Science, University of Melbourne; Department of Medicine, University of Melbourne

Background: Contact force (CF) during radiofrequency ablation (RFA) is an important determinant of endocardial lesion size with limited data on epicardial RFA and CF. We evaluated CF characteristics using irrigated RFA on the epicardium in an ovine beating heart model.

Methods: In 12 sheep a 7F irrigated RFA catheter with CF sensor was introduced via a small pericardial incision onto and in parallel with ventricular epicardium. RFA (30 watts/30 sec duration) with constant CF was applied at 5g, 10g, 20g, 40g and 70g over (a) left and right ventricular (LV/RV) myocardium at sites with or without fat; (b) either directly over or adjacent to a coronary artery; (c) directly over the phrenic nerve (PN) during PN pacing to assess for PN palsy. Each RF lesion size was measured and coronary artery and PN injury assessed.

Results: A progressive increase in lesion size and volume with higher CF was observed (p<0.05). Steam pops occurred with high CF. Epicardial fat had an insulating effect on RF penetration into myocardium (p<0.05); however RF lesions were created at sites with >3.5mm epicardial fat. At sites with epicardial fat, each 10g increment in CF led to a 0.6mm increase in myocardial lesion depth, while each 1mm of fat reduced lesion depth into underlying myocardium by 0.7mm. The extent of acute coronary injury with direct and indirect RFA, and the occurrence of PN palsy was proportional to CF.

Conclusion: CF is a determinant of epicardial RF lesion size, steam pops, acute coronary artery injury and PN injury. Although epicardial fat limits lesion size, RFA with high CF can produce small myocardial RF lesions at sites of thick epicardial fat.

**10 DR SARAH HANIEH**

THE EFFECT OF INTERMITTENT ANTENATAL IRON SUPPLEMENTATION ON INFANT OUTCOMES IN RURAL VIETNAM: A CLUSTER RANDOMISED TRIAL.

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Background: Iron deficiency anaemia remains a significant public health issue for pregnant women in rural South East Asia, with consequential high risks for maternal mortality, premature birth, low birth weight and poor maternal and infant outcomes. Compliance with currently recommended daily iron-folic acid supplementation (IFA) during pregnancy is poor. We compared the effects of twice weekly dosing of iron-folic acid or multiple micronutrients (MMN), with daily iron-folic acid supplementation during pregnancy, on maternal and infant outcomes in a rural province of Vietnam.

Methods: A cluster randomised controlled trial was conducted in Hanam Province, Vietnam. 104 communes were randomly assigned to one of three intervention arms, and 1258 pregnant women were enrolled into the study. Women received either one capsule of iron-folic acid per day (60mg iron/capsule); two capsules of iron-folic acid per week (60 mg elemental iron/capsule); or two capsules of multiple micronutrients per week (60mg iron/capsule). Primary outcome was infant birth weight.

Results: Mean birth weight was 3148 g [SD 416]. There was no difference in birthweights of infants of women receiving twice weekly IFA compared to daily IFA (mean difference (MD) 28 g; 95% CI -22 to 78), or twice weekly MMN compared to daily IFA (MD -36.8g; 95% CI -82 to 8.2).

Conclusions: Twice-weekly antenatal IFA or MMN did not result in a clinically important difference in birthweight, when compared to daily IFA supplementation. Intermittent antenatal IFA should be considered for use in populations with low rates of iron deficiency.

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INVESTIGATING PRACTICES RELATING TO MALNUTRITION IN VICTORIAN CANCER SERVICES: RESULTS FROM THE POINT PREVALENCE STUDY.

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Malnutrition is an important supportive care need for people with cancer. Malnutrition can be defined as unintentional weight loss with inadequate dietary intake and muscle or fat deficits. The causes of cancer malnutrition include metabolic abnormalities, the side effects of cancer treatment and mechanical issues, including obstruction by tumour. Cancer malnutrition is associated with reduced treatment tolerance and quality of life, increased complications, extended length of stay and higher health care costs.

The aims of this study were to determine the prevalence of cancer malnutrition in Victoria, identify the proportion of malnourished patients receiving dietetic intervention and the association between malnutrition and clinical outcomes at 30 days.

Method: In March 2012, a point prevalence malnutrition study of adult cancer patients was conducted in 15 Health Services in Victoria, including The Royal Melbourne Hospital City Campus (RMH). The patients were included from both inpatient and ambulatory settings (ambulatory chemotherapy and/or radiotherapy). Dietitians undertook the data collection using a validated screening tool (Malnutrition Screening Tool) and validated malnutrition assessment tool (Patient Generated Subjective Global Assessment). Outcomes were collected at day 30.

Results: State-wide a total of 1693 cancer patients were included, with 31% (n=523) identified as malnourished. Malnutrition prevalence of inpatients was 57% (191 of 336) and 32% of ambulatory chemotherapy patients (292 of 917). At RMH, 63 cancer patients were included; 30 inpatients and 33 chemotherapy day unit patients. The cancer malnutrition prevalence at RMH was 49%. There was no difference in the malnutrition prevalence of inpatients and ambulatory chemotherapy patients at RMH. Of those patients identified as malnourished 73 % of inpatients and 50% of ambulatory chemotherapy patients at RMH were receiving dietetic intervention. This is similar to the overall state-wide results. Patients with malnutrition had a significantly higher 30-day mortality (6% vs. 1%, p<0.001) and unplanned hospital admission/re-admission rate (38% vs. 12%, p<0.001). The mean length of stay was 20.3 ± 17.6 days for malnourished in-patients and 15.7 ± 11.8 days for well-nourished patients (p<0.001).

Conclusion: Malnutrition prevalence in cancer patients is dependent on tumour type and treatment modality and is associated with increased length of stay, mortality and unplanned hospital admissions. Identification of malnutrition with validated screening and assessment tools and appropriate dietetic resource allocation is essential to ensure patients receive appropriate and timely dietetic intervention. This project was funded by Victorian Government Department of Health through special project grants to each participating site.

IDENTIFYING RISK FACTORS FOR HYPOGLYCAEMIC EPISODES IN HOSPITAL INPATIENTS

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Background: Currently 30% of hospital inpatients have diabetes and this proportion is increasing. The management of inpatients with diabetes is challenging and hypoglycaemia is a serious event that can negatively affect the course of a patient’s illness and consume significant resources.

Aim: To determine the frequency and factors associated with hypoglycaemic episodes experienced by inpatients with diabetes.

Methods: A case control study was conducted of patients in the endocrinology/renal ward and two general medicine wards. Cases (n=36) were patients who experienced hypoglycaemia. Controls (n=34) were matched to cases by age, sex and duration of diabetes. Clinical information and dietary intake in the preceding 24 hours was compared.

Results: The mean age of the cases and controls were 72.8 and 73.7 years respectively. The proportions of males were 59% and 56% in the case and control groups, respectively. Mean duration of diabetes was 18 years in both groups. Of the 36 cases, 77% experienced more than one episode of hypoglycaemia. Odds ratios for the development of hypoglycaemia according to observed variables (odds ratio; p value) were: missing meals (2.23; 0.18) requiring a texture modified diet (1.78; 0.45), reduced oral intake (1.79; 0.31), requiring assistance to eat (2.05; 0.21), change in diabetes medications (2.09; 0.13), insulin treatment (2.76; 0.05), sliding scale insulin (0.55; 0.21), sulphonylureal medication (1.18; 0.74), cognitive impairment (1.33; 0.63). The calorie intake in both groups was similar. The carbohydrate intake in the case group was reduced however this was not statistically significant (p= 0.4).

Conclusion: Hypoglycaemia occurs frequently in the inpatient population with diabetes. This relatively small but intensive trial identified a number of factors which can potentially contribute to increased hypoglycemia risk. Several
of these factors could be modified with targeted quality improvement activities and organizational change. This audit will inform service improvement.

13  DR SHEENA SULLIVAN

EVIDENCE NOT SHOWN FOR WANING OF INFLUENZA VACCINE EFFECTIVENESS DURING THE 2012 INFLUENZA SEASON IN VICTORIA, AUSTRALIA

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Background: Vaccine effectiveness may wane with increasing time since vaccination

Methods: We used the Victorian sentinel general practitioner (GP) network to estimate vaccine effectiveness (VE) for trivalent inactivated vaccines in the 2012 season. We used a test-negative design where cases were ILL patients that tested positive for influenza and noncases were those who tested negative. Vaccination status was recorded by GPs. The VE was calculated as (1-OR)×100%. VE estimates were compared early versus late in the season, and also by time since vaccination. A selection of positive samples had their virus isolates assessed antigenically by haemagglutination inhibition assay and viruses from healthy adults who experienced a vaccine breakthrough were also analysed genetically.

Results: The adjusted VE estimate for any type of influenza was 45% (95%CI:8.67) and for H3 was 35% (95%CI:13.62). We observed a non-significant effect of waning VE by time since vaccination; for those vaccinated within 92 days of presentation VE was 39% (95%CI:-24.70), while for those vaccinated 93 or more days before presentation the VE was 21% (-76.65). Comparison of VE early versus late in the season was very sensitive to the cut off week chosen for analysis. Antigenic data suggested that low VE was not associated with poor vaccine match among the A(H3) viruses. However, genetic analysis suggested nucleotide substitutions in antigenic sites.

Conclusion: In 2012, the TIV provided moderate protection against influenza. Antigenic and genetic data can provide additional insight into understanding VE estimates.

14  MS LOUISE WEIR

DIRECT-TO-CT MODEL HALVED RMH STROKE THROMBOLYSIS DOOR-TO-NEEDLE TIMES TO 25 MINUTES IN JUST 4 MONTHS

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Background: The benefit of stroke thrombolysis (tPA) is highly time-dependent. The treatment should be given as early as possible to effectively salvage brain tissue and function. European, American and Australian stroke centres provide tPA on average at 75 minutes from patient arrival. The Helsinki model with the world-record median 20 minute door-to-needle time (DNT) was described in 2012. We tested implementing components of that model at the Royal Melbourne Hospital (RMH).

Methods: The existing RMH ‘code stroke’ model was evaluated and restructured in January-April 2012 to include key elements of the Helsinki model: 1) Ambulance pre-notification with patient details alerting the stroke team to meet the patient on arrival; 2) Patients transferred directly from triage onto the CT table on the ambulance stretcher and; 3) tPA delivered in CT immediately after imaging. We analysed our prospective, consecutive tPA registry for effects of these protocol changes on our DNT following implementation during business hours (8am-5pm Monday-Friday) from May 2012.

Results: There were 62 patients treated with tPA in the 10 months following the protocol change. Compared to 85 patients treated in 2011, the median (IQR) DNT was reduced from 61 (43-75) minutes to 46 (23-80) minutes (p=0.020). All of the effect came from the change in the in-hours DNT, down from 43 (33-59) to 25 (19-48) minutes (p=0.002), whilst the out-of-hours delays remained essentially unchanged, 67 (55-82) to 62 (44-104) minutes (p=0.982).

Conclusion: We demonstrated rapid improvement in our service up to world best practice standard during business hours. The reduction in delays corresponds on average to an equivalent of one month of extra disability-free life for each treated patient. With the cooperation of ambulance, emergency, and stroke teams we succeeded in the absence of a dedicated neurological emergency department or electronic patient records which are key features of the Finnish system. The next challenge is in providing the same service out-of-hours.

15  DR VILIJA JOKUBAITIS

PREDICTORS OF 12-MONTH CONFIRMED DISABILITY PROGRESSION AFTER ONSET OF CLINICALLY ISOLATED SYNDROME (CIS) SUGGESTIVE OF MULTIPLE SCLEROSIS
Objective: We assessed the relationship of demographic, clinical, CSF, MRI and treatment to time 12-month confirmed disability progression after a clinically isolated syndrome (CIS) in Multiple Sclerosis

Background: The first 12-month confirmed disability progression event after CIS onset likely reflects persistent MS-related disability. Predictors of long-term sustained disability progression at CIS onset are not well characterised in real world datasets, and potential treatment effects are uncertain.

Design/Methods: The MSBase Incident Study (MSBasis) is an ongoing observational prospective cohort study of CIS, and enrols patients from 59 MS centres worldwide. Data were aggregated in MSBase, including patient profile, date of CIS, expanded disability status scale (EDSS) score, and cerebral MRI. Other diagnostic tests were recorded if performed. Follow-up data included relapses, treatment changes and EDSS score. Predictors for time to 12-month 1 EDSS step (1.5 EDSS steps for baseline EDSS 0, 0.5 for baseline EDSS 6-6.5) confirmed progression were analysed using Weibull hazards regression.

Results: Of 3413 CIS patients, 1994 had complete evaluable datasets including onset MRI (median follow-up 3.0 years). Of these, 309 patients had a first 12-month sustained disability progression event and 1370 (69%) were exposed to at least one MS medication (DMT). Predictors of time to progression in multivariable analysis were adjusted for clinic location and included a baseline Kurtzke functional score of ≥2 in the pyramidal system (HR 1.44; 95% CI 1.09, 1.90; p = 0.011, relative to a score of 0-1), and exposure to DMT was protective (HR for interferon beta (IFB)-1a IM was 0.54; for IFB-1b 0.45; for IFB-1a SC 0.41 and for daily glatiramer acetate 0.33; all p<0.001; all compared to no treatment HR=1).

No MRI or CSF findings were independent predictors of time to progression.

Conclusions: Using survival analysis, the multicentre, multinational MSBasis study has identified independent predictors of first 12 month disability progression, including a strong protective effect of beta-interferon and glatiramer acetate.

RELAPSE INCIDENCE IN WOMEN AND MEN THROUGHOUT THE COURSE OF MULTIPLE SCLEROSIS: AN MSBASE COHORT STUDY

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Introduction: Only one large retrospective cohort study and several smaller analyses examined predictors of relapse incidence in multiple sclerosis (MS). Sex, age and MS duration were suggested as determinants of relapse activity. It is of interest, that while in relapsing-remitting MS women are overrepresented in the ratio of 3:1 to men, in primary progressive disease both sexes are represented equally. This implies that men may be more likely to be diagnosed with a progressive MS due to their lower relapse activity.

Aims: To evaluate effect of sex on the incidence of MS relapses. To assess the hypothesis that the female-to-male ratio increases gradually with relapse activity and that the primary progressive disease represents a non-relapsing extreme along this continuum. To directly compare effects of age and disease duration on relapse incidence.

Methods: Annualised relapse rates were calculated using the MSBase registry. Patients with incomplete data or less than one year of follow-up were excluded. Patients with primary progressive MS were only included in the sex ratio analysis. Relapse incidences over 40 years of MS or 70 years of age were compared between females and males with Andersen-Gill and Poisson models. Female-to-male ratios stratified by annual relapse count were evaluated across disease duration and patient age and compared between relapse-onset and primary progressive MS.

Results: Among 11,570 eligible patients with relapse-onset MS (82,552 patient-years), 48,362 relapses were recorded. Relapse frequency was 17.7% higher in females compared to males. Within the initial five years, the female-to-male ratio increased from 2.3:1 to 3.3:1 in patients with 0 to 24 relapses per year, respectively. The magnitude of this sex effect increased at longer disease duration and older age. However, the female-to-male ratio in patients with relapse-onset MS and zero relapses in any given year was double that of the patients with primary progressive MS. Patient age was a more important determinant of decline in relapse incidence than disease duration.

Conclusions: Females are predisposed to higher relapse activity than males. However, this sex-related effect does not explain the markedly lower female-to-male ratio in primary progressive MS. Decline in relapse activity over time is more closely related to patient age than disease duration. This information helps us better understand the effects of sex and time on relapse incidence and define progressive-onset MS as an entity distinct from the relapse-onset MS.
IMPACT OF AN EMERGENCY GENERAL SURGICAL SERVICE ON TIME TO THEATRE

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Purpose: In Australia, the number of emergency hospital admissions requiring surgery increases annually by 3.8%, reflecting the growing population and life expectancy. Acute general surgery has already been well described in Australia. This study aims to examine the outcome of a consultant-led general surgical emergency service on the time to theatre.

Methodology – An in-house consultant-led emergency general surgery (EGS) service was established at the Royal Melbourne Hospital (RMH) in February 2011. All emergency general surgical admissions for the same two 6-month periods before and after the introduction of the service were examined. Time to theatre was recorded by the hospital patient database system. There was no additional planned theatre access provided. Data was analysed using STATA v. 11 using chi squared test and binomial proportion test.

Results: Total admissions increased by 19% (3553, 4056; p<0.0001). The greatest increase in theatre cases came from cholecystectomy, appendicectomy and non-trauma laparotomy (an increase of 53%, 120% and 54%, respectively p=0.001) accounting for 14%, 48% and 12% of the workload. With the EGS service, appendicectomy occurred 3.7 hours sooner, perianal abscess drained nine hours sooner and diagnostic laparoscopy 21.6 hours sooner during an admission when compared to the previous year. There was a 47% reduction in the number of surgical procedures performed overnight with an increase in daytime cases.

Conclusion: The implementation of the EGS unit at RMH has brought changes that improve patient care and safety. Along with an increase in emergency presentations the time to theatre has decreased for appendicectomy, abscess drainage and diagnostic laparoscopy.

DOES CONSULTANT-LED CARE WITHIN AN ACUTE CARE SURGICAL UNIT IMPROVE PATIENT OUTCOMES AT A LEVEL 1 TRAUMA CENTRE?

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Purpose: In 2011 the Emergency General Surgery Service (EGS) was established in response to the increase in volume of acute general surgical and trauma cases, at Royal Melbourne Hospital, a Level 1 Trauma Centre. The aim is to assess the impact of EGS on length of stay and admission to the ward from the ED compared to the traditional model.

Methodology: A retrospective review of our prospective surgical audit database of patients admitted to the EGS service from February 2011 to January 2012 (48 week period) was performed compared to previous 48 weeks.

Results: A 73% increase was noted in the total number of admissions from 1193 (pre-EGS) to 2065 patients since the introduction of the EGS service. With inclusion of inpatient referrals (411 patients) and Trauma admissions (2047 patients), the EGS service managed 4523 patients during the study period. Hospital LOS was reduced from 5 to 4.1 days (18% reduction) and a 20% improvement was noted in the percentage of patients admitted from ED within 8 hours (49% vs 69%). The percentage of surgical cases conducted in hours was found to be 50%.

Conclusion: Early and increased consultant input reduces length of stay and time spent in the ED, despite the 73% increase in acute admissions during the introduction of the new service.
DTI TRACTOGRAPHY REVEALS CHANGES IN THE OPTIC RADIATIONS OF PATIENTS WITH PERSISTENT VISUAL IMPAIRMENT FOLLOWING SURGERY FOR OPTIC CHIASM COMPRESSION

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Introduction: Tumours such as pituitary adenomas and meningiomas can cause compression of the optic chiasm and lead to visual failure or visual field (VF) deficits. These tumours account for up to 10% of all intracranial tumours. Previous studies have shown that retinal nerve fibre layer (RNFL) thickness on optical coherence tomography (OCT) can predict visual recovery following surgery for optic chiasm compression, however no study has investigated the downstream changes in the visual pathway from compressive pathology. The MRI technique of diffusion tensor imaging (DTI) tractography allows non-invasive investigation of the white matter pathways in the human brain in-vivo and DTI tractography can be used to visualise the structure of the white matter tracts of the visual pathway such as the optic radiation (OR). This study uses DTI tractography biomarkers to investigate changes in the OR of patients with tumours causing optic chiasm compression.

Methods: Patients recruited to the study were divided into two groups based on visual status. The normal vision group (n=10) had no VF deficit and normal RNFL thickness. The abnormal vision group (n=7) had persistent VF deficit and RNFL thinning on OCT. Patients from both groups underwent a single additional MRI on a clinical 3 Tesla MRI scanner at the Royal Melbourne Hospital at least one year post surgery which included anatomical and DTI protocols. DTI tractography of bilateral ORs for each patient was performed and OR tractography images were analysed for anatomical and DTI parameters.

Results: The OR DTI tractography data from this study correlated well with previously published dissection and DTI tractography studies. Significant differences in the OR DTI tractography were observed in a number of anatomical measurements and DTI biomarkers between patients with normal and abnormal vision. Patients with abnormal vision had decreased area at the midpoint of the OR (p=0.001), decreased OR volume (p=0.003), decreased fractional anisotropy (p=0.01), increased radial diffusivity (p=0.02) and increased apparent diffusion coefficient (p=0.04) compared to patients with normal vision.

Discussion: Using DTI tractography biomarkers, this study demonstrates decreased OR integrity and OR atrophy in patients with persistent visual deficit following surgery for tumours causing optic chiasm compression and is the first study to demonstrate downstream changes in the visual pathway in these patients. Further studies utilizing DTI biomarkers may lead to improved visual outcomes in patients undergoing surgery for tumours causing optic chiasm compression.

THE ROLE OF TGF-B-SMAD1/5 SIGNALLING IN TUMOUR CELL ENDOTHELIALISATION

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Introduction: Many tumour cells have been reported to be able to generate non-endothelial cell-lined microvascular channels in vivo and in vitro, in which tumour cells behave like endothelial cells. Further evidences showed that a proportion of tumour endothelial cells were derived from tumour cells. TGF-β signalling is known to play an important role in tumour vascularization and has shown association with vasculogenic mimicry. However, the mechanism between TGF-β signalling and tumour cell endothelialisation at the molecular level has not been explored thoroughly.

Aim: To establish the cellular process of tumour cell endothelialisation and the molecular principle of gain of endothelial-specific TGF-β-Smad1/5 signalling as an underlying mechanism of endothelialisation of tumour cells.

Methods: TGF-β Smad1/5 signalling and Smad2/3 signalling were examined by Western Blot and luciferase assay. BRE-reporter and CAGA-reporter luciferase viruses were used to detect specific Smad1/5 and Smad2/3 activation respectively. In this study, a doxycycline-inducible Smad6 cell line was established in MDA231 cells to specifically modulate Smad1/5 signalling.

Results: TGF-β can enhance the MDA231 cell formation of microvasculature on matrigel. Matrigel potentially increased TGF-β Smad1/5 and Smad2/3 signalling. Such microvasculature in vitro was reduced by Smad6 virus, which inhibited endothelial-specific smad1/5 signalling, not smad2/3 signalling. A doxycycline-inducible Smad6 cell line was established in MDA231 cell line. The inhibitory effect on microvasculature on matrigel was also shown in this Smad6 inducible cell line.

Conclusion: MDA231 cells can form microvasculature on matrigel and such tumour cell endothelialisation is TGF-β-Smad1/5 signalling dependent.
MURINE ORTHOTOPIC BIOLUMINESCENT GLIOMA STEM CELL XENOGRAFT MODEL

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Glioblastoma multiforme (GBM) is the most common brain cancer with 1500 new cases per year in Australia. Despite modern treatment (surgery, chemotherapy and radiation) median survival is still only 12-16 months. Previous studies have failed to elucidate successful therapies as they use traditional homogeneous cell lines that are not representative of GBM. To address this problem, we have isolated a panel of patient-derived glioma stem cell (GSC) lines using stem cell culturing techniques. GSCs are a subpopulation of the tumour that have the ability to self-renew, differentiate into multiple tissue types and produce tumours in vivo. GSCs appear to produce more heterogeneous tumours that better reflect the infiltrative behaviour of human GBM. In addition, orthotopic animal models provide important information regarding the ability of candidate drugs to cross the blood brain barrier which is another reason for treatment failure. By using multiple GSC lines (characterised for their molecular and genetic mutations) within our in vivo model we will also obtain invaluable insights into the progression of GBM and pathways involved in its growth and infiltration. The human GSC lines are engineered to express the luciferase (luc-2 firefly gene) protein to allow real-time in vivo tumour assessments using the IVIS (bioluminescent) live animal imaging system. By harnessing the IVIS system we are able to a) monitor early tumour development, b) quantify tumour burden in live animals, c) track treatment responses non-invasively, d) monitor animal health by tracking tumour burden, and e) significantly reduce animal numbers due to the ability to capture intermediate time point data in live animals. This model uses randomised 6-8 week female balb/c nu/nu mice that undergo stereotactic intracranial GSC implantation to the right frontal lobe. Mice are imaged at least weekly using the IVIS system to monitor tumour growth. We have thus established a murine orthotopic bioluminescent GSC xenograft model that allows real-time live tracking of in vivo GBM growth which is histologically consistent with human GBM. This model demonstrates log-linear growth kinetics that also allows tumour growth prediction/tracking. The model’s future applications include testing novel therapies for GBM and investigating its molecular and cellular characteristics.

TGF-B AND AUTOIMMUNE DISEASES IN HUMAN AND MICE

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Introduction: Transforming growth factor-β (TGF-β) negatively regulates immune responses. TGF-β signaling transduction requires the liberation of active TGF-β from latent complex. Evidences have revealed TGF-β might associate with both innate and adaptive function in autoimmune diseases. However, an accurate active TGF-β evaluating method is lacking and the correlation between active TGF-β and autoimmune disease has not been explored well.

Methods: In this study, we created a TGF-β luciferase reporter cell line with stable pCAGA(12)-luc expression for active TGF-β determination. We assessed serum active TGF-β levels in patients with systemic lupus erythematosus (SLE) (n=19), rheumatoid arthritis (RA) (n=12), systemic sclerosis (SS) (n=15), systemic sclerosis plus fibrosis (SS+F) (n=8) and dermatomyositis (DM) (n=9) and healthy controls (HC) (n=6). Serum active TGF-β levels were also determined in autoimmune-prone mice that resemble human SLE compared with the wide type (WT): ie. SHIP-/- (n=25) and WT (n=24) C57BL/6, and Lyn-/- (n=28) and WT (n=28) BALB/c. Analysis of variance (ANOVA) was performed among different groups; T-test was performed among every two groups.

Results: The TGF-β luciferase reporter cell line detected active TGF-β in serum samples with high sensitivity. SLE patients showed significantly decreased serum active TGF-β levels than healthy controls (p=0.0023). Reduced active TGF-β levels were also found in SHIP-/- mice in comparison with C57BL/6 WT (p<0.0001). There is no difference of active TGF-β levels between young (10 weeks) Lyn-/- and WT BALB/c. Aged (40 weeks) WT BALB/c mice showed significantly higher active TGF-β levels than the young WT (p<0.0001), however, aged Lyn-/- mice had similar low levels as young age WT and Lyn-/-.

Conclusion: Low active TGF-β levels were found in patients with SLE and in mice resembling human SLE. These evidences suggest that reduction of active TGF-β might associate with the onset of SLE and highlight the possibility of active TGF-β to be a biomarker and therapeutic target of SLE. There is also an age-associated increase of serum active TGF-β in the WT BALB/c mice; suggesting that TGF-β may associate with age-related declines of immune responsiveness.
THE TKS5 ADAPTOR PROTEIN – A REGULATOR OF INVADOPODIUM FUNCTION AND METASTASIS IN CANCER CELLS

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The cause of death for up to 90% of cancer patients is the metastatic spread of cancer cells from the primary tumour and the subsequent development of a secondary tumour or tumours at a distant site. Many patients normally present with symptoms relating to the localized primary disease which can be managed with a number of therapies including surgery, radiation and chemotherapy. But numerous patients return post-therapy with a developed metastatic lesion at a secondary site. The dissemination of metastatic cells involving the migration and infiltration of these invasive cells is commonly thought to require two events. This includes increased cellular motility, accompanied with the proteolytic processing of the extracellular matrix (ECM) and subsequent penetration through extracellular tissues occurring prior to the patient presenting with the primary tumour.

A property shared by several types of tumour cells with high invasive or metastatic potential is an ability to form structures known as invadopodia. They are dynamic actin-rich protrusions which adhere to and proteolytically degrade ECM substrates via the activities of numerous transmembrane and secreted extracellular proteases. Functional (matrix-degrading) invadopodia have been observed in tumour cell lines and primary tumour cells derived from ex vivo tumour specimens from a number of cancers, primarily head and neck squamous cell carcinoma and breast cancer specimens. This suggests that there is a possible role for invadopodia in tumour cell invasion.

Src tyrosine kinase and Tks5 (an adaptor protein with PX and SH3 domains) are central mediators of invadopodia formation. However, it was not known until recently, when we showed that Tks5 can co-localize to invadopodia with F-actin, through a co-operative relationship with Src and the Nck adaptor proteins to subsequently regulate cellular actin dynamics and promote ECM degradation. Consistent with the biogenesis of invadopodia, we have shown that Tks5 overexpression leads to a striking and selective increase in the secretion of matrix metalloproteinases. We were also the first to demonstrate that Tks5 expression in patient tumour samples can predict reduced survival (Stylli et al (2012) Prognostic significance of Tks5 expression in gliomas. J. Clin Neurosci, 19(3):436-442). In addition, we have utilized an immunohistochemical approach to determine the Tks5 expression profile of various cancers in human cancer tissue microarrays. We detected varying levels of Tks5 in all cancer samples with increased expression over the corresponding normal tissue, suggesting that Tks5 may play an important role in the invasion process of tumour cells.

SPECIFIC INHIBITION OF BCL-2 BY ABT-199 AS TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Aims: ABT-199, a Bcl-2 selective inhibitor is being developed for CLL, a disease commonly characterised by Bcl-2 overexpression. The specific aims of this work are to: (i) determine the in vitro sensitivity of CLL to ABT-199, (ii) compare this with the in vitro sensitivity of normal donor cells, (iii) define the effect of ABT-199 on CLL in vivo as part of the first-in-human phase I clinical trial underway at Royal Melbourne Hospital (RMH) for patients with relapsed / refractory CLL.

Methods: Peripheral blood (PB) and bone marrow (BM) (n = 43) from patients with CLL and PB from normal donors (n = 8) were cultured in the presence of ABT-199 for 24 hours and cell death assessed by failure of propidium iodide exclusion detected flow cytometrically. IC50 (half maximal inhibitory concentration) was calculated for CLL and normal cells (granulocytes, B and T lymphocytes [CD4, CD8]). In vivo effects of ABT-199 were assessed by monitoring PB counts and phosphatidylserine (PS) exposure flow cytometrically. CLL response was assessed against standard criteria (IWCLL 2008). Results: CLL demonstrates high in vitro sensitivity to ABT-199 (median IC50 1.1nM; 95% CI mean 0.8 – 21nM). While normal B lymphocytes have similar sensitivity to ABT-199 (mean IC50 3.2nM; 95% CI 0.6 – 5.7nM; p>0.05), CD4 (mean IC50 2676nM; 95% CI 949 – 4403nM; p<0.0001) and CD8 (mean IC50 1400nM; 95% CI 325 – 3137nM; p<0.0001) T lymphocytes are significantly less sensitive and granulocytes very insensitive (mean IC50 >5000nM; p<0.0001). In patients, rapid reductions in circulating CLL cells were observed after a single dose of ABT-199 (20 – 200mg), and laboratory evidence of tumour lysis without clinical sequelae was seen in 3/15. Increased PS exposure was demonstrated for PB CLL cells collected 6 – 24 hours after in vivo dosing with ABT-199. With ongoing dosing (100 – 600mg/day), 14/15 CLL patients at RMH have demonstrated clinical responses (67% partial, 27% complete) and no subject has required withdrawal due to toxicity.
Discussion: These in vitro and clinical findings indicate significant efficacy of ABT-199 against CLL. The preliminary clinical results demonstrate impressive and rapid responses in relapsed/refractory disease. Consistent with the purported mechanism of action, our data indicate that ABT-199 is inducing CLL apoptosis in vivo. The initial clinical trial of ABT-199 is ongoing and will report the toxicities and durability of clinical responses when completed. Additional clinical trials of ABT-199 alone and in combination with other agents have commenced in patients with CLL.

25 DR JULIANNE BAYLISS

HEPATITIS B SPLICING IS ENHANCED PRIOR TO DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

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Introduction: The mechanisms through which chronic hepatitis B virus (HBV) infection causes hepatocellular carcinoma (HCC) are unknown. Evidence suggests that splicing of the HBV pregenome, resulting in the generation of spliced HBV (spHBV) variants may increase viral replication and protein production, in turn promoting tumourigenesis. In this study we have determined the profile of serum spHBV in patients with chronic liver disease and HCC and analysed changes in spHBV over time; providing the first longitudinal analysis of spHBV in relation to the development of HCC.

Methods: Two hundred and eighty seven serial serum samples were collected from 165 patients with chronic HBV monoinfection, including 58 patients who later developed HCC. Clinical parameters for each patient collected included; antiviral drug treatment, standard liver function tests and model for end stage liver disease (MELD) and Child-Pugh scores for severity of liver disease. Where available, liver biopsy specimens were also obtained and graded for fibrosis via METAVIR. All patients (HCC and HCC-free) were on antiviral treatment. Real time PCR was used to amplify and quantify wt and sp DNA loads.

Results: spHBV was detected in over 80% of patients with chronic HBV infection. Median serum spHBV levels were significantly higher in HCC patients than HCC-free control patients (6.693% (0-60.89%) vs. 0.424% (0-26.68%) for HCC and HCC-free respectively; p<0.001). When spHBV was compared in HCC and HCC-free controls with severe fibrosis (F3/4), median serum spHBV was significantly higher in the HCC patients than HCC-free controls (8.567% (1.47%-60.89%) vs. 0.61% (0-26.68%) for HCC and HCC-free respectively; p=0.001). Univariate analysis revealed a strong correlation between time to HCC diagnosis and spHBV DNA levels (τ=0.203; p=0.016). Asian HBV genotype (p=0.025) and increased viral load (p<0.001) were also significantly associated with increased spHBV DNA levels. Multiple regression analysis revealed time to diagnosis of HCC, Asian HBV genotypes and viral load to be associated with increased spHBV DNA (model p<0.001; R2=0.189). Further, for every single percentage increase in serum spHBV, patients were more than six times as likely to be diagnosed with HCC (OR=6.12; 95% CI=1.68-10.56; p=0.007).

Conclusions: HBV splicing is a common event during chronic infection and increases prior to diagnosis of HCC. Measurement of HBV splicing may prove a valuable adjunct to be used in the identification of chronically infected patients who are at increased risk of developing HCC.

26 DR HAMED ASADI

MACHINE LEARNING FOR STROKE OUTCOME PREDICTION

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BACKGROUND: Stroke is a major cause of death and disability. Accurately predicting stroke outcome from a set of predictive variables is an important aspect of clinical work, which can assist in identifying high-risk patients and guide treatment approaches, thus potentially decreasing mortality.

For dichotomised outcomes, the usual approach is to develop logistic regression models; however, machine learning algorithms using artificial neural networks have been proposed as an alternative, with the outstanding advantage of self-improvement via feedback.

Our aim was to design an artificial neural network, capable of predicting the outcome of an acute stroke, by proposing a binary measure.

METHODS: Using MATLAB, a two-layer feed-forward network, with sigmoid hidden and output neurons, was designed to classify predictor vectors, into potential good and poor outcomes, as per arbitrarily dichotomized 30 day modified Rankin Scale, with ten neurons in its hidden layer.

The network was then trained, with scaled conjugate gradient back-propagation, and subsequently validated and tested using randomly divided data from 70 prospectively collected cases, with the final performance monitored with mean squared error.

This preliminary model will be integrated into a software package, ready for further testing and training.


RESULTS: Age, Gender, Involved Artery, IV-tPA, T2-DM, HTN, H-Chol, AF, IHD, TIA, NIHSS, and TICI, were some of the predictive factors included in our model. Available cases were divided into 70, 15 and 15% for training, validation and testing, and the network was trained. Best validation performance of 0.24 was achieved at 10th epoch, in <1 second with gradient of 0.096 and validation check of 6 at epoch 16. The final confusion matrix, demonstrated a congruency of ~90% between the Target and Output Classes, with a favourable Receiving Operative Characteristic. CONCLUSIONS: Numerous factors can influence the final stroke outcome with varying significance and mechanisms, making conventional modelling challenging and perhaps inaccurate. On the other hand, machine learning models with neural network algorithms, relatively independent of the unknown potential underlying interactions between these factors, are able to simulate the eventual result of such a complex system. As well, these models, can be used as a tool in predicting the outcome under different circumstances, and be used as a potential assistant in decision making regarding a variety of possible treatment options. FUTURE WORK: The final goal of this study is to provide a robust self improving model which can perceivably optimise the process of selecting endovascular versus medical treatment in acute stroke.

27 MS CAMILA BATTISTUZZO

EFFECTS OF TREADMILL TRAINING ON HINDLimb MUSCLE PROPERTIES IN SPINAL CORD INJURED MICE

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Muscle fibre type conversion and atrophy is observed in animal models of spinal cord injury (SCI). Exercise is known to prevent some of these changes, however, the training duration required to optimize recovery has not been investigated. Purpose: To examine the effect of 3 and 6 wks of exercise on hindlimb muscle properties after SCI. Method: Adult mice (C57Bl/6) received a left spinal hemisection and then were assigned to untrained and trained (10 min treadmill, 5 x wk for 3 or 6 weeks) groups. Mice were sacrificed (100 mg/kg, i.p. ketamine, decapitation) and the medial gastrocnemius (MG), soleus (SOL) and tibialis anterior (TA) muscles were removed from left (injured) and right (uninjured) hindlimbs. ATPase histochemistry was used to assess muscle properties. Digital images were captured and analysed with Image J software and data were compared using analysis of variance and Tukey post hoc tests. Significance was set at P > 0.05. Results: Fiber type composition and fiber area were not altered in SOL and TA muscles in either limb of 3 (n = 4) or 6 wks (n = 4) trained and untrained animals. Fibre type composition was also unaltered in MG, however, fibre type IIB area was 33% larger in MG from the injured-limb vs. uninjured limb after 6 wks of training. The area of type IIX fibres was also larger in MG muscles from the injured vs. uninjured side in 6-wk trained animals. Conclusion: Six weeks of treadmill training selectively reduces atrophy in type IIB and IIX fibres in the fast twitch gastrocnemius muscle.

28 MS ELIZABETH BOWMAN

LONGITUDINAL REDUCTIONS IN CEREBELLAR VOLUME IN ADULT-ONSET NIEMANN-PICK DISEASE TYPE C.

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Niemann-Pick disease type C (NPC) is a rare, progressive neurometabolic disorder characterized by disruptions in sterol trafficking. The adult-onset form of the disease often presents with neuropsychiatric symptoms such as psychosis and cognitive difficulties, and later with ataxia, dystonia and supranuclear gaze palsy. Frequently, it is initially misdiagnosed as schizophrenia or a related psychotic disorder. NPC also shares certain neuropathological features such as neurofibrillary tangles with other neurodegenerative diseases such as Alzheimer’s disease. Previous research has demonstrated that subcortical regions are likely to be affected first, and most severely, by the disease process. This study has investigated changes to cerebellar grey and white matter volume in a population of adult-onset NPC patients. T1-weighted magnetic resonance imaging scans from nine adult-onset NPC patients aged 18 to 49, and 17 age- and gender-matched healthy controls, underwent automatic segmentation using the FreeSurfer longitudinal analysis pipeline. NPC patients were followed up for an average of 44 months, and controls for an average of 72 months. Eight of the nine NPC patients were receiving substrate-reduction treatment using Miglustat, and pre-treatment scans were
also available for one NPC patient. Linear rate of loss of cerebellar grey and white matter volume was compared between participant groups, and between untreated and treated patients.

On average, control participants were found to lose 43.4 mm³/month of cerebellar grey matter, and treated NPC patients lost volume at a rate of 87.2 mm³/month (p = 0.088). However, the mean rate of volume lost for NPC patients not receiving Miglustat treatment was 410.7 mm³/month, significantly more than both treated patients (p < 0.001) and controls (p = 0.0001). Cerebellar white matter changes were found to be much more variable, with controls found to have a mean increase of 0.584 mm³/month, and treated NPC patients an increase of 8.1 mm³/month. This was not significantly different (p = 0.549), however untreated NPC patients were found to have a mean decrease in volume of 191.9 mm³/month. Again, this was significantly different to both controls (p = 0.0001) and treated patients (p = 0.017).

This is the largest longitudinal cohort of adult-onset Niemann-Pick disease type C in the world, and the first to demonstrate the potential protective effect of Miglustat treatment on human cerebellar neurons. Current work involves further exploration of the longitudinal effects of treatment on behavioural measures of disease severity such as ataxia and saccadic eye movements.

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DR BRUCE CAMPBELL

EXTENDING THE TIME FOR THROMBOLYSIS IN EMERGENCY NEUROLOGICAL DEFICITS – INTRA-ARTERIAL: THE EXTEND-IA TRIAL RATIONALE AND PROTOCOL


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Background: The proven benefits of tPA within 4.5 hours of stroke onset are limited by modest reperfusion rates in patients with major vessel occlusion. Endovascular mechanical clot retrieval may increase reperfusion rates in these patients.

Aim: EXTEND-IA will test the hypothesis that dual target vessel occlusion and penumbra mismatch can select patients with favourable response to reperfusion using mechanical clot retrieval after standard IV tPA<4.5hrs from stroke onset.

Methods: EXTEND-IA is a prospective, randomised, open-label, blinded-endpoint (PROBE) phase 2 trial of mechanical clot retrieval (Solitaire device) after IV tPA vs tPA alone in 100 patients with ischemic stroke <4.5 hours from onset. Eligibility for the trial requires vessel occlusion of the ICA or MCA (M1/M2) and CT or MR “mismatch” using a perfusion threshold of Tmax>6sec and a perfusion:infarct core lesion volume ratio of >1.2. Infarct core volume, assessed using MR-DWI or CT-relative cerebral blood flow, must be <70mL. This is assessed using a fully automated software package (RAPID, Stanford University). The co-primary endpoint is reperfusion at 24hr and favourable clinical response (≥8 point reduction in National Institutes of Health Stroke Scale or reaching 0) at 3 days with secondary endpoints including recanalization, symptomatic hemorrhage and functional outcome (modified Rankin score at 90 days).

Results: Recruitment has commenced at 8 centres in Australia and New Zealand with a further 6 sites planned to open in 2013.

Conclusions: EXTEND-IA will provide much needed randomized evidence about the effectiveness of clot retrieval in a responder population defined by CT or MR mismatch.

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DR WENJIE CAO

CAN ACUTE LACUNAR INFARCTION BE DIAGNOSED USING CT PERFUSION?

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Background and purpose: The value of CT perfusion (CTP) in detecting acute lacunar infarcts (LACI) has not been well established. We tested the sensitivity of CTP images for identification of LACI in the acute phase.

Methods -- CTP of consecutive acute ischemic stroke patients admitted to Royal Melbourne Hospital between 2009 to 2013 was examined to identify those with MRI-confirmed LACI (single perforating vessel territory). Two stroke neurologists, blinded to the MRI, independently evaluated the CTP maps. Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF), Mean Transit Time (MTT) and Time to maximum (Tmax) maps were first examined in isolation and then in combination. Interobserver agreement was measured using Cohen k. Raters then reached consensus. The lesions identified were later confirmed against MRI by consensus of 3 raters. The sensitivity of CTP maps using DWI as the reference standard was calculated. Fisher exact test was performed to compare map types.
Results -- There were 30 patients with MRI-confirmed LACI within the coverage of CTP, 17 in the basal ganglia, 9 thalamic, 4 in the corona radiata. Interater agreement was substantial (κ = 0.65). Sensitivity (blinded consensus) was highest for MTT (40%) compared to Tmax (16.7%, p = 0.006). CBV (3%) and CBF (3%) performed poorly. There were no false positives. Sensitivity was higher for external basal ganglia lesions than thalamic lesions (53% vs 11%, p = 0.037).

Conclusions -- MTT maps enable detection of a significant proportion of LACI using CTP. Further study is required to determine whether CTP positive versus negative lacunes have different clinical outcomes.

31 DR PABLO CASILLAS-ESPINOSA

A NOVEL T-TYPE CALCIUM CHANNEL ANTAGONIST DELAYS THE PROGRESSION OF EPILEPTOGENESIS IN THE AMYGDALA KINDLING MODEL OF TEMPORAL LOBE EPILEPSY

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Purpose: Temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults that is refractory to medical treatment. Current therapeutic treatment is symptomatic, suppressing seizures, but has no disease modifying effect on epileptogenesis. T-type Ca2+ channels have been implicated in pathogenesis of limbic epileptogenesis, therefore the current study set out to investigate the effects of a novel T-type Ca2+ channel antagonist (Z944, Zalicus Pharmaceuticals) on the progression of epileptogenesis in the amygdala kindling model of TLE. We have previously shown that Z944 was not effective at suppressing seizures in fully kindled rats.

Methods: Female non-epileptic rats underwent surgery to implant a bipolar electrode into the left amygdala for electrical kindling as well as subdural EEG recording electrodes. Post-surgery, animals received Z944 (30mg/kg) (n=7), ethosuximide (ETX, 100mg/kg) (n=6) or vehicle (n=6) 30 minutes prior to each kindling stimulation up to a maximum of 30 stimulations. For molecular analysis, mRNA expression levels were assessed in the hippocampus using qPCR for Cav3.1, total Cav3.2, +/- exon 25 splice variants, and Cav3.3. Results: Animals receiving Z944 required more stimulations to evoke a class III, IV or V seizure and to reach a fully kindled state than animals receiving ETX or vehicle. There was no significant difference in Cav3.1, total Cav3.2, +/-25 or -25 or Cav3.3 mRNA expression in the hippocampus between the three treatment groups.

Conclusion: These results provide evidence that T-type Ca2+ channels are important in limbic epileptogenesis and that drugs that target these channels may represent a new therapeutic intervention to prevent the progression of limbic epilepsy.

32 MR JIANXIONG CHAN

INCREASED SUSCEPTIBILITY TO THE DEVELOPMENT OF EPILEPSY IN A MOUSE MODEL OF ALZHEIMER DISEASE

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Background: Alzheimer disease (AD) is the most common cause of dementia. Seizures occur in up to 64% of people with AD during their course of illness, imposing additional burden on medical care and disability. Recurrent seizures and their treatment with conventional antiepileptic drugs may exacerbate the progression of AD. There are no specific treatments for seizures in AD patients. The relationship between the pathological processes of AD and neuronal hyperexcitability is poorly understood, partly owing to the absence of a specific animal model of epileptogenesis in AD. This project aimed to better understand the relationship between AD pathology and seizure susceptibility by developing a specific model of acquired epileptogenesis in AD. We hypothesised that the pathological changes of AD in themselves lower seizure threshold, as well as increase the susceptibility to the development of epilepsy secondary to brain insults.

Methods: Tg2576 APP mutant mice and wild-type (WT) mice were subject to electrical amygdala kindling. The Tg2576 APP mutant mouse is a well-established AD model showing correlative behavioural, biochemical and pathological abnormalities with AD in human, while electrical amygdala kindling is an established model of acquired temporal lobe epilepsy in which repeated stimulations were applied to the amygdala complex. The sensitivity to the development of epilepsy was compared between the mutant and WT mice.

Result: Tg2576 APP mutant mice reached the fully kindled stage with fewer stimulations compared with WT (n=5 per group; average number of stimulations (Tg2576 vs. WT); 3.8 [SD 3.47] vs. 11.4 [SD 3.62]; p=0.0072). Seizure severity at each stimulation was significantly greater and the seizure duration longer in the Tg2576 APP mice compared with WT.

Conclusion: Tg2576 APP mutant mice have increased susceptibility to the development of acquired epilepsy. This represents a potentially novel model of acquired epileptogenesis in AD for research to better understand the...
relationship between AD pathology and epileptogenesis, and to develop more effective and safer treatments tailored to AD patients with epilepsy and ultimately interventions to prevent the development of epilepsy in AD patients.

### 33 DR CHRIS FRENCH

**COMPUTATIONAL APPROACHES FOR MODELLING NEUROLOGICAL DISORDERS AND DRUG EFFECTS**

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In the last few decades, major advances have been made both in the understanding of neuronal function as well as computing and software capabilities. The combination of these two advances is known as computational neuroscience. This new methodology not only allows realistic simulations of neural networks, but also permits even atomic scale simulations of drug interactions with receptors on nerve cells. We have used these approaches to model normal and epileptic brain tissue. Additionally, we have commenced atomic level modelling of a common epileptic drug, phenytoin, with its neural receptor, the voltage gated sodium channel. This modelling allows us to explore pathological neural behaviour and drug action at a scale very difficult to achieve in a conventional biological preparation. It is also yielding new and unexpected insights into how drugs interact with a receptor, so providing new avenues for development of better, more effective drugs.

### 34 DR MELISSA GRESLE

**DO MULTIPLE SCLEROSIS RISK SNPS INFLUENCE GENE EXPRESSION IN IMMUNE CELLS?**

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In recent times, large scale genome wide association studies have identified and confirmed more than 40 genetic variants, or single nucleotide polymorphisms (SNPs), that are associated with a modest increase in risk of MS. MS associated risk SNPs are not found within protein coding regions (exons) of the DNA, but rather, they are found in untranslated sequences including promoter regions or introns. Hence, the influence of these risk variants on biological functions, are largely unknown. We hypothesise that MS risk SNPs will promote immune cell subtype specific gene expression changes, to influence immune cell function.

We are using gene expression and genotype data to identify if MS risk alleles are associated with the differential expression of nearby genes, known as “cis-eQTL”, in common immune cell subsets. We have recruited 101 healthy controls and 74 MS patients (of relapsing-remitting phenotype, less than 10 years disease duration). From each, 100ml of venous blood was collected and monocyte, NK cell, B cell, CD4+ and CD8+ T-cells were isolated using magnetic beads for positive selection. For each cell subtype, RNA was purified, and then hybridized on Affymetrix Human Exon 1.0 ST arrays. DNA was also isolated from buffy coats and samples genotyped using a custom-designed chip that includes all known MS loci.

To date, we have analysed data for a subset of monocyte (48 cases and 40 controls) and NK cell (32 cases and 37 controls) samples. For eQTL analyses, we used a list of 72 SNPs that were associated with MS or showed suggestive association, and for each SNP, we identified genes within 110kb upstream and 40kb downstream of the transcription end site. For each SNP-expressed gene pair, we tested whether gene expression was associated with number of risk alleles of the SNP, and also assessed association with case/control status. Results were highly discordant between monocytes and NK cells. In monocytes, 14 eQTL associations were significant at P < 2x10-4 (the Bonferroni-corrected significant p-value for 241 individual tests), whereas none of the NK eQTL met this threshold. Of particular interest is the fact that 3 of these 14 eQTLs are also, after adjusting for genotype, differentially expressed in MS cases versus controls.

Importantly, these preliminary studies suggest that some MS risk alleles could influence the expression of nearby genes in a cell specific manner. We are currently investigating how these gene expression changes could alter immune function to increase the risk of MS.

### 35 DR NIGEL JONES

**GAMMA FREQUENCY NEURAL OSCILLATIONS AND PREPULSE INHIBITION: A CASE OF SIGNAL-TO-NOISE?**

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Gamma frequency neural oscillations and prepulse inhibition: a case of signal-to-noise?
Purpose: An emerging literature implicates abnormalities in gamma frequency neural oscillations in the symptoms of schizophrenia. Prepulse inhibition (PPI) is a behavioural measure of sensorimotor gating, and is disrupted in schizophrenia patients. Here we studied the relationship between gamma frequency oscillations and PPI, with the hypothesis being that increasing gamma power would lead to an increased ‘noise’ in neural circuits and disrupt PPI.

Methods: Adult Wistar rats (n=7) were surgically implanted with extradural recording electrodes. Rats were connected to EEG cables, and placed into PPI chambers, facilitating simultaneous EEG and behavioural measurement. Rats received sc injection of either Ketamine (5mg/kg), MK801 (0.08mg/kg), amphetamine (0.5mg/kg), LY379268 (0.3mg/kg) or vehicle (saline) and were subjected to 90 minutes of PPI trials and EEG recording. Outcomes were measured every 5 minutes.

Results: Administration of the 3 psychotomimetic compounds (ketamine, MK801, amphetamine) led to an increase in the power of gamma oscillations and a time-matched disruption of PPI. The three drugs had different kinetics: ketamine showed a rapid onset and offset (within 30 min) of action, MK801 a slowly developing but prolonged effect (>90min), whereas amphetamine elicited a delayed response which was less pronounced than the NMDA receptor antagonists. In contrast, the mGlur agonist LY379268 significantly reduced gamma power, but also disrupted PPI suggesting a dichotomy between behaviour and neural oscillations.

Conclusion: The contrasting effects of the drugs studied here (all disrupted PPI but had differing effects on gamma power) is suggestive of a complex relationship between neural oscillations and sensorimotor behaviour. Psychotomimetic drugs increase gamma frequency noise which may be causal to the observed disruption of PPI, whereas LY379268 may be dampening the signal itself.

36 DR TOMAS KALINCIK

CLINICAL PRESENTATIONS OF MULTIPLE SCLEROSIS RELAPSES ARE ASSOCIATED WITH PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

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Introduction: Our knowledge of incidence and outcomes of multiple sclerosis (MS) relapses with specific neurological presentations is limited. For example, optic neuritis is more common in early disease stages and the capacity of the neurological functions to recover deteriorates with longer disease duration. However, a comprehensive evaluation of multiple sclerosis relapse phenotypes, comprising clinical presentations, severity, impact and recovery, and capturing full spectrum of MS courses, duration and patient demography, has not yet been done.

Aim: To identify patterns of clinical MS relapses, their impact on specific neurological functions and their associations with demographic and clinical parameters.

Methods

Information about clinical presentations of relapses was collected prospectively in 17,555 eligible patients and 104,333 patient-years recorded in MSBase, an international observational multiple sclerosis registry. In a proportion of the relapses, information about relapse severity, impact on activities of daily living and recovery was available. Associations between relapse phenotype and patient characteristics were tested with a series of multivariable logistic regression models. Principal component analysis was conducted to assess the tendency of the specific relapse types to occur concurrently in individual patients.

Results

Of the recorded 63,343 relapses, majority affected pyramidal and sensory functions. Visual and brainstem relapses occurred more frequently in early disease stages and in younger patients. Sensory relapses were recorded mostly in earlier disease and less commonly in relapsing-progressive disease. Pyramidal, sphincter and cerebellar relapses were more common in older patients and in progressive disease. Women more commonly presented with sensory or visual symptoms, while men were more prone to pyramidal, brainstem and cerebellar relapses. Relapses were likely to recur within the previously affected neurological domains, with pyramidal, sphincter and sensory relapses often converging within the same individuals. Sensory relapses had a lower impact and together with visual and brainstem relapses showed better recovery than the other relapse presentations. Finally, relapse severity increased and the ability to recover decreased with age or more advanced disease.

Conclusions

Relapses show typical patterns of clinical presentations, which depend on demographic and clinical factors, including age, sex, disease duration, course and stage. This information may improve our vigilance over the more likely relapse types in individual patients.
AMYGDALA KINDLING DECREASES PROTEIN PHOSPHATASE 2A (PP2A) ACTIVITY AND INCREASES PHOSPHORYLATED TAU, AND ACTIVATING PP2A WITH SODIUM SELENATE SUPPRESSES EPILEPTOGENESIS

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The epilepsies are a group of common brain diseases. Current anti-epileptic drugs do not mitigate the processes that convert a healthy brain into an epileptic brain, i.e. epileptogenesis, nor modify the underlying disease processes once established. Protein phosphatase 2A (PP2A) regulates key signalling pathways in the brain, and down-regulation of PP2A increases pathologically phosphorylated tau (p-tau) in neurodegenerative diseases, suggesting that this may play a pathogenic role in these disorders. To investigate the role of PP2A in epileptogenesis and the effects of a specific PP2A activator on epileptogenesis, we utilized amygdala kindling in rats as an in vivo model of limbic epileptogenesis. We found that PP2A activity and expression levels of the PP2A 55kDa regulatory subunit B (PR55) were significantly decreased and that concomitantly, p-tau on Ser 198 and 262 were increased in the amygdala, hippocampus and cortex of amygdala kindled rats compared with the same brain sections of sham kindled rats. Furthermore chronic treatment with sodium selenate, a specific PP2A activator, significantly slowed the behavioural and electrographic progression of amygdala kindling, compared with those treated with NaCl. Selenate-treated kindled rats had significantly increased PP2A activity and PR55 expression, and decreased p-tau on Ser 198 and 262, in these regions compared with rats treated with NaCl. These results indicate that amygdala kindling epileptogenesis is associated with a down-regulation of PP2A activity and an increase in p-tau, and that pharmacologically enhancing PP2A activity with sodium selenate is a potentially viable anti-epileptogenic therapeutic strategy.

HEMIPLEGIC SHOULDER PAIN IN ACUTE STROKE

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Questions: What is the incidence of hemiplegic shoulder pain in acute stroke patients? Is a risk assessment score predictive for the development of pain? What factors are associated with development of hemiplegic shoulder pain?

Design: Prospective observational study. Participants: One hundred consecutive stroke patients were included from the Royal Melbourne Hospital Stroke Unit. Outcomes: Risk of hemiplegic shoulder pain was assessed with the Management Tool for Acute Hemiplegic Shoulder (MTAHS). Other measures included the Mobility Scale for Acute Stroke (MSAS) and the Modified Rankin Scale. Results: 6% of patients developed hemiplegic shoulder pain during their admission. Patients scoring high risk assessed by the MTAHS on admission had a significant chance of developing pain (p = 0.003). There was also a significant association between being scored high risk on the MTAHS and the occurrence of severe physical impairment assessed by the MSAS (p = 0.000). Length of hospital stay was significantly associated with incidence of pain on discharge (p = 0.0004). The median length of stay for those without pain was seven days [IQR 5-11]; compared with those with pain, whose median length of stay was 17 days [IQR 14-22]. Conclusion: The use of the MTAHS risk assessment tool could assist in identifying which patients need to be targeted by physiotherapists and occupational therapists for ongoing management strategies to prevent development of hemiplegic shoulder pain to minimise the consequences of this as time progresses.

WHOLEBRAIN CT PERFUSION PREDICTS POST-STROKE HAEMORRHAGIC TRANSFORMATION

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Background: Intracerebral haemorrhage is the most serious potential complication of stroke thrombolysis. MRI studies have shown that diffusion lesion volume predicts haemorrhagic transformation after stroke. We sought to determine the optimal CT perfusion (CTP) parameter for prediction of cerebral parenchymal haemorrhage (PH) in acute ischemic stroke.

Methods: Patients with acute ischemic stroke with onset <9 hours had whole-brain CTP, followed by follow-up CT/MRI to determine presence or absence of haemorrhagic transformation. Receiver operator characteristic (ROC) analysis was performed to determine the optimal level of relative cerebral blood flow (rCBF) and relative cerebral blood
Glioblastoma multiforme (GBM) is the most common and lethal form of brain tumour, and despite intensive research efforts, still portends a dismal prognosis. Among the deadliest of all human cancers, GBM is characterized as a highly diffuse and infiltrative disease, and retains almost 100% mortality. GBM is thought by many to be driven and sustained by a small subset of slow-cycling cancer ‘stem cells’ (CSCs) within the tumour that are resistant to current treatment modalities. CSCs have self-renewal capability, akin to normal human stem cells, and may possess other traits also seen in their ‘normal’ counterparts, such as slow cell cycle progression, and resistance to chemo- and radiotherapy. Isolation of this fraction of recalcitrant cell population would allow tailored research, but markers for CSCs remain elusive. Stem cell markers such as CD133 have been employed somewhat successfully to enrich for these cancer stem cells, but to date have failed to reliably and consistently pinpoint an expression profile that represents a true cancer stem cell phenotype. The real test of cancer cell ‘stemness’ thus remains a function of slow cell cycle, and in vivo, to identify novel therapeutic targets for GBM treatment. It is hoped that genetic screens of treatment responsive and treatment resistant and treatment-responsive patient biopsies will yield clinically meaningful differences that may guide novel treatment regimens, leading to more favourable patient outcomes.

Validation of Stem Cells Using Division Rates and Marker Expression in Glioma

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Glioblastoma multiforme (GBM) is the most common and lethal form of brain tumour, and despite intensive research efforts, still portends a dismal prognosis. Among the deadliest of all human cancers, GBM is characterized as a highly diffuse and infiltrative disease, and retains almost 100% mortality. GBM is thought by many to be driven and sustained by a small subset of slow-cycling cancer ‘stem cells’ (CSCs) within the tumour that are resistant to current treatment modalities. CSCs have self-renewal capability, akin to normal human stem cells, and may possess other traits also seen in their ‘normal’ counterparts, such as slow cell cycle progression, and resistance to chemo- and radiotherapy. Isolation of this fraction of recalcitrant cell population would allow tailored research, but markers for CSCs remain elusive. Stem cell markers such as CD133 have been employed somewhat successfully to enrich for these cancer stem cells, but to date have failed to reliably and consistently pinpoint an expression profile that represents a true cancer stem cell phenotype. The real test of cancer cell ‘stemness’ thus remains a functional one (pluripotency, the ability to recapitulate an organ or tumour). We therefore aim to isolate glioblastoma stem cells from cultured cell lines and fresh patient biopsies using a pulse-chase assay with fluorescent intracellular dyes that the cell dilutes with each cell division. Based on their slower division rates, CSCs should retain the dye longer than non-CSCs, and be able to be isolated by FACS sorting. Once such a population has been isolated, we aim to analyse their stem cell marker expression, gene expression, protein expression, and resistance to the oral alkylating agent, Temozolomide, in vitro and in vivo, to identify novel therapeutic targets for GBM treatment. It is hoped that genetic screens of treatment-resistant and treatment-responsive patient biopsies will yield clinically meaningful differences that may guide novel treatment regimes, leading to more favourable patient outcomes.

Overcoming Challenges in Conducting Rare Cancer Research: CART-WHEEL.org Experience with a Rare Ovarian Cancer Study

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Overcoming Challenges in Conducting Rare Cancer Research: CART-WHEEL.org experience with a Rare Ovarian Cancer Study

Background: www.CART-WHEEL.org was established to facilitate rare cancer research by partnering with people affected by rare cancers and ensuring adequate clinical data collection for researchers. A study focusing on high-grade mucinous ovarian cancer is the first proof of principle study demonstrating the need for collaboration between multiple sites, clinicians, scientists, and cancer consumers.

High-grade mucinous ovarian cancer (HG-MOC) is a rare subtype of epithelial ovarian cancer (EOC), occurring in young women. Traditionally, HG-MOC has been treated with the standard platinum-based treatment used for advanced stage EOC, however, HG-MOC are usually drug resistant, with high patient mortality. Controversy exists over whether HG-MOCs are in fact metastases from a distant site. www.CART-WHEEL.org is facilitating a study to characterise the molecular profile of HG-MOC in comparison to mucinous cancers from extra-ovarian sites.

Methods: Multiple approaches are being used to identify adequate numbers of appropriate tissue samples for the study. Cases of rare HG-MOC will be identified via www.Cart-Wheel.org and via national and international tissue
banks. FFPE blocks will be obtained for pathologic review and immunohistochemical analysis and HER2 in situ hybridization performed. Using genome-wide technologies the molecular profile of HG-MOC will be compared to mucinous cancers from extra-ovarian sites, such as colon/rectum, stomach and primary appendiceal pseudomyxoma peritonei, as well as borderline and low grade MOCs. Results: Practical difficulties encountered in accessing cases of a rare cancer type will be discussed, in particular, the crippling ethical and governance issues involved in sourcing a small number of cases from a large number of sites. Baseline characteristics of HG-MOC and control cases will be described. RNASeq data has been generated from a pilot set of MOC and mucinous cancers from colon, gastric and appendix primary sites and relevant molecular profiles will be reported. Conclusion: Ongoing challenges exist in coordinating the process of identifying cases of rare cancers, obtaining ethical and governance approval and tissue retrieval before any molecular testing can take place. Satisfying requirements at different institutions causes delays which often prevent the undertaking of such research. However, rare cancer research may define genetic aberrations leading to a better molecular understanding of more common diseases. Comparisons between HG-MOC and mucinous cancers from extra-ovarian sites could result in a change in future therapeutic approaches and clinical trial design for this cancer subtype.

43 MR MUN YOONG CHEANG

CT SCAN OR LUNG PALPATION IN THE DETECTION OF PULMONARY METASTASES: A SYSTEMATIC REVIEW

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INTRODUCTION: Several studies have illustrated the generally low sensitivity of CT scans in detecting nodules (67 – 93%) and thus some have purported intra-operative palpation as the gold standard for identification of nodules. This is a systematic review of studies which have directly compared CT scanning with intra-operative palpation. Through a meta-analysis we aim to provide estimated sensitivity of CT scanning in identifying lung metastasis pre-operatively.

METHOD: The study followed the PRISMA protocol for systematic reviews and meta-analyses. The search strategy included an electronic literature review using the PubMed database. The MeSH terms utilised were pulmonary metastasectomy, CT, lung palpation, thoracoscopic and open. For articles to be included they were required to be in English and human research. Article types excluded from the review included letters and editorials, and referenced unpublished data. Inclusion criteria included the need for articles to compare CT scanning to intra-operative palpation. The studies should clearly state true positive and false negative either on the basis of individual nodules detected or on the basis of each operative case. The search yielded 11 relevant papers.

RESULTS: Eleven studies with 610 patients fulfilled the inclusion criteria. An analysis inclusive of all metastases reveals a pooled sensitivity of 81% of pre-operative CT in identifying metastatic disease (95% CI 78 – 84%). This data however is statistically significant for heterogeneity (I2 = 81.4%, p < 0.01). For tumours <5mm, pooled sensitivity across studies was 62% (95% CI 52 – 71%) but this data was statistically significant for heterogeneity (I2 = 81.1%, p = 0.0051). For tumours 6 – 10mm, pooled sensitivity was 72% (95% CI 60 – 83%) and this data was not significantly heterogenous (I2 = 49.7%, p = 0.1370). For tumours >10mm in diameter, sensitivity of pre-operative CT was 99%. This data was not statistically significant for heterogeneity (p = 0.07). Pre-operative CT scanning in identifying clinical cases with any metastatic disease demonstrated a pooled sensitivity of 85% (95% CI 76-91%) and the data was not statistically significant for heterogeneity (I2 = 26.8%, p=0.255). The pooled prevalence of cases in which CT underestimates the number of metastases in the lungs is 20% (95% CI 12 – 30%). This data however is heterogenous (I2 = 83%, p < 0.01). CONCLUSION: In conclusion, CT underestimates a significant number of metastases and lung palpation remains the gold standard in identifying lung nodules.

44 MR MUN YOONG CHEANG

PULMONARY METASTASECTOMY BY VATS OR OPEN THORACOTOMY: A SYSTEMATIC REVIEW

Pradyumna Herle, Mun Yoong Cheang, Akshat Saxena, Phillip Antippa
The Royal Melbourne Hospital

INTRODUCTION

VATS has become an increasingly popular technique for the cardiothoracic surgeon. Its use in the treatment of malignancy has been an issue of debate previously. Whilst its use has been documented for the treatment of primary lung cancers, its use in metastasectomy has been brought under question for several reasons. The low sensitivity of pre-operative CT in diagnosis of metastatic disease in the lungs, compared to palpation means that VATS may miss resection of metastatic lesions. VATS has also been associated with pleural and port site seeding. Whilst there have been several studies demonstrating roughly equivalent survival and more rapid post-operative recovery in minimally invasive approaches, there remains no randomised trials and other high level evidence.
regarding the oncological outcomes of VATS versus open thoracotomy for pulmonary metastases. This article attempts to provide a systematic review of studies which have directly compared open and VATS resection of pulmonary metastasis in terms of outcome.

METHOD: The study followed the PRISMA protocol for systematic reviews and meta-analyses. The search strategy included an electronic literature review using the PubMed database. The MeSH terms utilised were pulmonary metastasectomy, VATS, thoracoscopic and open. The inclusion criteria for the studies are that they had to have 2 limbs for direct comparison of VATS and open thoracotomies. The studies must also provide data regarding overall survival data or recurrence free survival data separately for the 2 limbs of the study.

RESULTS: Nine studies with 796 patients fulfilled the inclusion criteria. The VATS groups had slightly higher odds of 1, 3 and 5 year survival with OR of 1.53, 1.69 and 1.41 respectively. All these results demonstrated no heterogeneity on testing. However, only 3 year survival was statistically significant for overall effect. The VATS group also had higher odds of 1, 3 and 5 year recurrence free survival with OR of 1.29, 1.54 and 1.54 respectively for each of these outcomes. Once again the tests demonstrated no significant heterogeneity on testing. None of the outcomes demonstrated statistical significance in testing for overall effect.

Overall pulmonary recurrence had lower odds in the VATS group with an odds ratio of 0.55. This data was not significantly heterogenous (p = 0.15) and did not demonstrate statistical significance in testing for overall effect also (p = 0.28).

CONCLUSION: Outcomes from VATS are comparable to, if not better than, open thoracotomy. VATS is a suitable choice for pulmonary metastasectomy.

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**45 DR GIOVANNA D’ABACO**

**INHIBITION OF FOCAL ADHESION KINASE IN GLIOMA STEM CELLS PREVENTS NEUROSphere FORMATION AND LEADS TO CYTOTOXICITY**

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Glioblastoma multiforme (GBM) is a highly invasive brain tumor in which expression of Focal Adhesion Kinase (FAK) has been shown to play a role. After interaction with integrin, FAK drives signaling pathways that regulate cell growth, shape, polarity and migration. We explored the role of FAK using patient-derived glioma stem cell neurosphere cultures, which may provide a better model for testing novel therapies. We found that levels of phosphorylated FAK are elevated in glioma stem cell lines and that treatment with Y15, a small molecule inhibitor of FAK (1,2,4,5-Benzotetraamine, 4HCl) significantly inhibited neurosphere formation and led to cell detachment, apoptosis and cell death. Furthermore, Y15 led to cell death in the CD133+ glioma stem cell subpopulation, whereas treatment with the standard chemotherapeutic agent temozolomide did not. These results suggest that targeting FAK may be a stem cell-specific therapeutic strategy in the treatment of glioblastoma.

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**46 MS KATIE DOAN**

**IS EARLY INTEGRATION OF PALLIATIVE CARE FOR PATIENTS WITH INCURABLE LUNG CANCER ACCEPTABLE TO AUSTRALIAN HEALTHCARE PROFESSIONALS?**

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Lung cancer is the leading cause of death from cancer in Australia. In a recent landmark US study, metastatic NSCLC patients who received palliative care from the time of diagnosis concurrently with standard oncology management reported improvements in quality-of-life, symptom control, reduction in “aggressive therapies” at end-of-life, and a survival advantage compared to those receiving standard oncology management alone. In Australia, it is unclear what the views of clinicians who care for patients with incurable lung cancer are about routine early integration of palliative care.

This qualitative sub-study is part of a larger three phase Early Integration of Palliative Care in Oncology (EIPCO) project. The aim of the sub-study was to explore health care professionals’ perceptions of EIPCO for patients with incurable lung cancer. Three focus groups and six interviews were conducted with 28 health care professionals (doctors, nurses and allied health professionals) working in three large metropolitan teaching hospitals in Melbourne. Participants were asked to describe barriers and facilitators to implementation of a model of care involving EIPCO for patients with incurable lung cancer.

The following four key themes were identified:

1. Trust;
Early and routine involvement of palliative care in patients with incurable lung cancer is acceptable to the majority of treating clinicians. Palliative care services must be embedded in the system, sufficiently resourced and of high quality. For early referral to occur it is important that the model also involves a physical presence of a palliative care clinician in clinic who is easily accessible for referrals and provides treating clinicians with the tools they need to understand what Palliative Care have to offer as well as the language to be able to effectively introduce Palliative Care to patients and their carers.

PERCEPTIONS AND ATTITUDES TO EARLY INTEGRATION OF PALLIATIVE CARE FOR PATIENTS WITH INCURABLE LUNG CANCER: RESULTS OF A SURVEY.

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Lung cancer is the leading cause of death from cancer in Australia with the majority of patients diagnosed with late stage incurable disease. Although there is evidence of patient benefit from early involvement with specialist palliative care, this may not translate into clinical practice.

The aim of this study was to explore clinicians' perceptions and attitudes to Palliative Care referral. A modified validated self-report questionnaire (Johnson, 2008) was given to clinicians (doctors, nurses and allied health) involved in the care of patients with incurable lung cancer, working in the multi-disciplinary lung cancer teams at three teaching hospitals in metropolitan Melbourne. 55 questionnaires were distributed and 42 completed (76% response rate).

93% of respondents agreed that early referral to Palliative Care is beneficial to patients and 95% agreed that Palliative Care can benefit patients receiving active treatment. However, only 60% of respondents agreed that all advanced cancer patients should be referred to Palliative Care. When asked for the main reasons for not referring to Palliative Care, 60% agreed they do not refer when the patient has no symptoms and 60% agreed they do not refer if they can manage the patients' symptoms themselves. However, just 38% of clinicians agreed they were well trained to take care of the symptoms of advanced cancer patients. Issues related to patients not understanding or accepting their prognosis were cited as barriers to referral by a third of clinicians.

Clinicians involved in the care of patients with incurable lung cancer have positive perceptions and attitudes to Palliative Care but this may not translate into routine referral of all patients with incurable lung cancer. In order to make referral routine, we need education around the perception that only patients with unmanageable symptoms benefit from referral to Palliative Care. In addition, further training of clinicians about symptom management appears desirable.


FIRST-LINE CLINICAL TRIALS AND METASTATIC COLORECTAL CANCER: HOW SELECTED ARE CLINICAL TRIAL PARTICIPANTS?

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Background: Guidelines recommend that oncology patients have the opportunity to participate in a clinical trial wherever possible. It is purported that as trial participants are often younger and fitter, data extrapolation from trial outcomes to patients seen in routine care may be difficult. We compared characteristics of patients with metastatic colorectal cancer (mCRC) participating in a first-line clinical trial with those treated in routine care.

Methods: The TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) database, a clinician-designed mCRC comprehensive database, was used to identify patients treated on a first-line trial compared with those receiving
combination chemotherapy; single-agent therapy; or no chemotherapy. Data collection began in June 2009 and is ongoing at fifteen Australian centres to date.

Results: Of 671 patients, 49 (7.3%) participated in a first-line clinical trial. Patients on trial were significantly younger, with 49% (n=24) trial participants being under 60 years, compared with 33% (n=128) receiving combination chemotherapy off study (p=0.047), 13% (n=13) single-agent therapy (p<0.0001) and 10% (n=15) no treatment (p<0.0001). All trial participants were ECOG performance status 0-1, compared with 87% (n=335) of non-trial patients receiving combination chemotherapy (p<0.0001), 80% (n=82) receiving single-agent therapy (p<0.0001) and 52% (n=76) no treatment (p<0.0001). Similarly, Charlson comorbidity score was significantly lower in trial participants, with 88% (n=43) having a score 0-3 (less comorbidity) versus 71% (n=272) receiving combination chemotherapy, 39% (n=40) receiving single-agent therapy and 25% (n=36) no treatment. Preliminary analysis suggests significant overall survival benefit for the clinical trial cohort.

Conclusions: Consistent with the available literature, trial participants with mCRC are significantly younger, fitter and of better performance status than those who receive similar chemotherapy off-trial or no treatment. The impact of trial participation on survival may be thus subject to multiple factors biasing for a better outcome, including the contributing benefit of younger age and less comorbidity.

49 DR KATHRYN FIELD

METASTATIC COLORECTAL CANCER AND MANAGEMENT IN PUBLIC VERSUS PRIVATE HOSPITALS: SIMILARITIES AND DIFFERENCES.

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Background: Potential differences between public and private cancer care in Australia include the degree of subspecialisation, multidisciplinary clinic review, access to clinical trials and continuity of care, all of which could impact treatment and outcomes. Here we compared demographics, tumour details, treatment and survival outcomes for patients (pts) with newly diagnosed metastatic colorectal cancer (mCRC) treated in the public versus private setting.

Methods: This research was conducted using the TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) mCRC clinical research database. Data collection began in June 2009 and is ongoing at 15 Australian centres. Here, data from four public and eight private hospitals are presented.

Results: Of 671 patients, 253 (38%) were treated at public hospitals and 418 (62%) at private centres. For public versus private pts there was no significant difference in median age or percentage with good performance status. More private pts received first-line chemotherapy (89% vs 80%, p=0.002), but there were no significant difference in the use of bevacizumab (50% versus 43%, p=0.10). Similar proportions received combination therapy (72% private vs 68% public) but the use of single agent oral capecitabine was higher for private patients (9% vs 4%, p=0.03). More public pts were enrolled in a first-line clinical trial (17.3% vs 1.2%, p<0.0001). Preliminary analysis suggests improved overall survival for private pts (26 months versus 17 months, p<0.001).

Conclusions: While public and private pts in this cohort were similar in age and performance status, significantly more private pts were given chemotherapy, but similar proportions were given bevacizumab and far less were enrolled on first-line clinical trials. This may relate to availability of first-line trials during this period. The superior survival outcomes achieved in private practice must be further explored, and might reflect a more intense approach to treatment, yet-to-be identified differences in patient characteristics, or differences in quality of care.

50 DR KATHRYN FIELD

PATTERNS OF CARE ACCORDING TO TREATMENT INTENT FOR METASTATIC COLORECTAL CANCER: A 3-YEAR REVIEW OF ROUTINE PRACTICE.

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5 Medical Oncology, Cabrini Health, Malvern, Victoria, Australia
6 Medical Oncology, Royal Brisbane Hospital, Brisbane, Queensland, Australia
7 Medical Oncology, Royal Hobart Hospital, Hobart, Tasmania, Australia
Background: Cure is potentially achievable in a small percentage of patients (pts) with metastatic colorectal cancer (mCRC). The treatment approach in routine practice for such pts is unknown, with uncertainty regarding the optimal timing and content of adjuvant treatment.

Methods: The TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) database recording information on pts diagnosed with mCRC since July 2009 from 12 Australian centres was analysed. Management strategies for pts where a curative-intent resection had occurred; was planned; or was a potential option were compared with those managed with palliative intent.

Results: Of 550 patients, when first reviewed by a medical oncologist, 46 (8%) had already undergone curative-intent resection; 53 (10%) had resection planned; 59 (11%) were considered potentially resectable if response to treatment was good; and 383 (70%) were treated with palliative intent. Chemotherapy was ultimately delivered in 74% (n=34) of already-resected pts, 87% (n=46) planned for resection, 95% (n=56) potentially-resectable and 76% (n=292) palliative-intent pts. 26% (n=9) already-resected pts also received bevacizumab, compared with 45% (n=46) planned or potentially-curative pts and 61% (n=179) treated with palliative intent. At the time of analysis 24 pts (45%) with a planned resection and 17 (29%) considered potentially curative have had surgery, while 7 (2%) where treatment was initially considered palliative have had curative-intent surgery. Of all 68 pts who have undergone curative-intent resection, 50% (n=34) received neoadjuvant chemotherapy. Overall, 60 (88%) had an R0 resection.

Conclusions: Treatment strategies for mCRC are varied according to treatment intent. Bevacizumab was less likely to be used for already-resected pts. A significant minority of resected patients do not receive chemotherapy. Many initially considered resectable had yet to undergo resection; which will be explored further. Conversely, occasional ‘palliative’ pts may become resectable, confirming the importance of continued review of this option.

51 DR KATHRYN FIELD

MALIGNANT GliOMA IN REGIONAL AND RURAL COMMUNITIES: COMMUNICATION, EDUCATION AND NEEDS

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Aims: Patients with malignant glioma are usually managed in neurosurgical tertiary referral centres; however 30% return to their regional/rural location for ongoing care. This study explored levels of communication, education and the needs of patients and doctors.

Methods: A survey was designed, targeting regional/rural oncologists, general practitioners (GPs) and patients with malignant glioma. The survey was funded by a WCMICS grant. Questions to doctors included: adequacy of referral information, access to services, and areas they would like to improve knowledge skills. Patient questions included: information provided at diagnosis; access to medical services; and improved clinical support.

Results: The overall response rate was 49% (8 oncologists, 30 GPs, 9 patients). 70% of GPs felt the information received from the hospital was ‘adequate’ or ‘excellent’. Doctors sought: improved communication and support regarding clinical decision making (multi-disciplinary care); education regarding the use of dexamethasone, antiepileptics, novel therapies and recommendations regarding driving. 37% of GPs had “low”: confidence in managing patients with malignant gliomas. 78% of patients felt they were provided ‘enough’ information at diagnosis. The three most comprehensive information sources for patients were their surgeon; medical oncologist; and radiation oncologist. 56% of patients requested improved carer support and 67% would seek initial assistance from their GP for any issue related to their brain tumour.

Conclusions: While communication between the tertiary hospital and regional/rural centres is occurring consistently, we have identified a number of areas where clinical care can be improved. An action plan is being developed to address educational needs for regional/rural doctors, and additional information provision for patients and their carers.

52 DR KATHRYN FIELD

UNDERSTANDING WHO CAN DRIVE AND WHO SHOULD MAKE THE DECISION: A SURVEY OF GLIOMA PATIENTS AND THEIR DOCTORS.

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Aims: Understanding which glioma patients can drive and who should make the decision is a critical component of ongoing care. Government legislation varies across jurisdiction and is less well articulated for the glioma group.
compared to head injury and epilepsy patients. This study examined glioma patient and doctor understanding of driving recommendations as well as the level of communication between doctors and patients.

Methods: We surveyed medical and radiation oncologists, general practitioners (GPs), and patients with malignant glioma in regional and rural centres. Patients were identified from our clinical database and a questionnaire developed with input from relevant groups including: consumers, surgeons, oncologists and allied health specialists. The surveys were completed in the last quarter of 2011. The project was funded by a WMCICS grant.

Results: The overall response rate was 49% (total responders: 8 oncologists, 30 GPs and 9 patients). Less than 50% of surveyed clinicians routinely discuss driving issues with their patients. One-third of surveyed clinicians rated themselves as ‘not very confident’ in their ability to advise patients about driving. One-third of surveyed patients stated that no-one had advised them about driving, and 50% stated that they were not certain whether or not they were permitted to drive, despite holding a licence.

Conclusions: This project has identified several concerning issues in the communication and understanding of driving for patients with brain tumours. Treating doctors have low levels of confidence in advising patients and a substantial proportion of patients are unclear whether they may or may not drive. These issues should be urgently addressed, and action plans are in development.

53 MS CATHERINE GRANGER

PHYSICAL ACTIVITY LEVELS OF INDIVIDUALS WITH NON-SMALL CELL LUNG CANCER

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Context: Research demonstrates that improved functional capacity gained by increased physical activity (PA) may be associated with improved survival in non-small cell lung cancer (NSCLC). However there is limited investigation of the PA levels of people with NSCLC. Aims: In people with NSCLC to 1) identify levels of PA, functional capacity, strength and patient reported outcomes at time of diagnosis, and compare these with PA guidelines and healthy aged-matched individuals, and 2) measure changes over six months from diagnosis. Methods: 50 participants (32 male) from three tertiary hospitals (Royal Melbourne Hospital, Peter McCallum Cancer Centre, Austin Hospital) with stage I–III NSCLC, mean ± standard deviation (SD) age 68±9years were assessed at diagnosis (prior to treatment), at 10 weeks (during chemo/radiotherapy) and at six months. 35 community dwelling individuals (19 male), mean ± SD age 63±9years without cancer were assessed once. Significant between group differences existed for age (p=0.005). Measures included accelerometery and global position satellite tracking (steps per day, outdoor walking time), strength tests, functional capacity [six minute walk test (6MWT)] and questionnaires [self-reported PA, nutrition, mood, exercise motivation, environmental PA barriers and health related quality of life (HRQoL)]. Statistical analyses included between group comparisons using analysis-of-covariance to control for age differences or Mann-Whitney U tests as appropriate. Linear mixed models were used to assess change over time in the NSCLC group. Results: Only 40% of participants with NSCLC met PA guidelines at diagnosis. Mean ± SD steps per day were 586±62990 and median [IQR] outdoor walking time was 7 minutes [0 to 35minutes]. Compared with community dwelling participants, objective PA and self-reported PA in participants with NSCLC at time of diagnosis were significantly reduced [steps per day mean difference 2363, 95%CI 685 to 4041, p=0.007] and [self-reported PA, p=0.0005]. Significant between group differences were also found in quadriceps strength (p=0.032), nutrition (p<0.0005), depression (p=0.027) and motivation to exercise (p=0.001); but not in anxiety (p=0.296) or environmental PA barriers (p=0.155-0.746). Over six months participants experienced decline in self-reported PA (p=0.010) but not in steps per day (p=0.986). Participants also experienced decline in quadriceps strength (p<0.0005). Number of steps per day was moderately correlated with 6MWT (r=0.560) and nutritional status (r=0.463). Conclusion: At diagnosis, individuals with NSCLC engage in less PA, are weaker and more depressed than healthy individuals and their self-reported PA declines over six months. Funding: Victorian Cancer Agency and Eirene Lucas Foundation.

54 DR RODNEY LUWOR

IDENTIFYING NOVEL PROGNOSTIC MARKERS AND MEDIATORS OF Glioblastoma Multiforme PROGRESSION AND RESISTANCE TO TEMOZOLOMIDE

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Glioblastoma Multiforme (GBM) is the most aggressive and lethal primary brain tumour due to its highly invasive and neurologically destructive characteristics. Maximal tumour debulking is vital although the highly invasive nature of GBM means that microscopic disease is inevitably present, making surgical cure impossible. The pivotal study by the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical
Trials Group (NCIC) showed that the addition of the oral alkylating agent, temozolomide (TMZ) to standard post-operative radiotherapy resulted in a significant improvement in survival compared to radiotherapy alone (median survival 14.6 vs 12.1 months, hazard ration 0.63, p<0.0001). Longer-term follow-up has shown that 5 year survival increased from 1.9% to 9.8%.

Many strategies are being pursued to improve the outcomes of these patients, with the most common being the addition of newer agents to the backbone of surgery and chemo-radiation as per the EORTC-NCIC protocol. To date, none have shown additional benefit and all have shown additional toxicity. An alternative approach is to identify biomarkers that would enrich for GBM patients most likely to benefit from surgery and chemo-radiation. Therefore, it is critical to identify the key genetic and molecular alterations promoting GBM development, progression and resistance to therapy.

We aim to utilise differential gene expression profiles using both retrospective and prospective approaches to identify novel predictors of GBM patient survival and resistance to temozolomide. We hypothesise that several genes identified to be either up-regulated or down-regulated in our recent gene expression microarray analysis of GBM patient tumour samples may indeed predict patient survival outcome and temozolomide response.

Our preliminary analysis of tumour samples (taken from patients having their first surgical resection and who had received TMZ treatment post-surgery) using the genome-wide gene expression microarray chip, Human HT-12 v4 (which allows for analysis of expression of over 47,000 genes) revealed that 44 genes were significantly reduced (less than 1.5 fold; p< 0.05) and 56 genes were significantly enhanced (greater than 1.5 fold; p< 0.05) from short-term survivors (mean survival 185 ± 12 days post-surgery) compared to long-term survivors (mean survival – 857 ± 149 days post-surgery). This work forms the foundation for future studies to identify potentially novel predictive prognostic markers for patient survival and TMZ resistance.

MURINE ORTHOTOPIC BIOLUMINESCENT GLIOMA STEM CELL XENOGRAFT MODEL

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Glioblastoma multiforme (GBM) is the most common brain cancer with 1500 new cases per year in Australia. Despite modern treatment (surgery, chemotherapy and radiation) median survival is still only 12-16months. Previous studies have failed to elucidate successful therapies as they use traditional homogeneous cell lines that are not representative of GBM. To address this problem, we have isolated a panel of patient-derived glioma stem cell (GSC) lines using stem cell culturing techniques. GSCs are a subpopulation of the tumour that have the ability to self-renew, differentiate into multiple tissue types and produce tumours in vivo. GSCs appear to produce more heterogeneous tumours that better reflect the infiltrative behaviour of human GBM. In addition, orthotopic animal models provide important information regarding the ability of candidate drugs to cross the blood brain barrier which is another reason for treatment failure. By using multiple GSC lines (characterised for their molecular and genetic mutations) within our in vivo model we will also obtain invaluable insights into the progression of GBM and pathways involved in driving its growth and infiltration. The human GSC lines are engineered to express the luciferase (luc-2 firefly gene) protein to allow real-time in vivo tumour assessments using the IVIS (bioluminescent) live animal imaging system. By harnessing the IVIS system we are able to a) monitor early tumour development, b) quantify tumour burden in live animals, c) track treatment responses non-invasively, d) monitor animal health by tracking tumour burden, and e) significantly reduce animal numbers due to the ability to capture intermediate time point data in live animals.

This model uses randomised 6-8wk old female babl-c nu/nu mice that undergo stereotactic intracranial GSC implantation to the right frontal lobe. Mice are imaged at least weekly using the IVIS system to monitor tumour growth. We have thus established a murine orthotopic bioluminescent GSC xenograft model that allows real-time live tracking of in vivo GBM growth which is histologically consistent with human GBM. This model demonstrates logarithmic growth kinetics that also allows tumour growth prediction/tracking. The model’s future applications include testing novel therapies for GBM and investigating its molecular and cellular characteristics.

A ROLE FOR WNT IN COLORECTAL CANCER MORPHOGENESIS

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Wnt/beta-catenin signaling has multiple functions throughout gut development and homeostatic control of the intestinal epithelium. Aberrant activation of the Wnt pathway is observed in over 90% of human colorectal cancers (CRC) and it is now evident that this aberrant activation plays pivotal roles in the initiation, growth and progression of...
CRC. Our findings implicate that FZD7 transmits Wnt signals in both normal intestinal epithelium and in CRC. Investigating the latter, we established a CRC morphogenesis model (LIM1863-Mph) that forms multicellular organoids resembling encased carcinoma tubules. The LIM1863-Mph organoids contain several intestinal epithelium cell types; including goblet cells, enterocytes and LGR5+ undifferentiated cells. They also recapitulate many features of the phenotypic transitions that underlie tumor morphogenesis, invasion and metastasis. We showed FZD7 is required for tubular patterning of the LIM1863-Mph organoids by knocking it down using shRNAi. It is also required for migration of the mesenchymal adherent cells. Superarray analysis of transcript levels in organoid and monolayer cells showed an increase in Wnt2b and Wnt11 levels in the organoids, thereby implicating these Wnts in tubular patterning. To investigate their role in tubular patterning of the organoids and cell migration, we used shRNAi again. Reduction of Wnt11 levels in LIM1863-Mph cells, leads to morphological changes in organoid cultures that resemble mini cotton wool-like structures. Reduction of Wnt11 and Wnt2b levels leads to morphological changes in monolayer cultures that also resemble mini cotton wool-like structures. The phenotypes we observe are consistent with Wnt2b and Wnt11 co-operating with FZD7 in establishing the architecture of the organoids. It is already known that Wnt11 binds FZD7; via co-immunoprecipitation we show an interaction between Wnt2b and FZD7. Another avenue to investigate the Wnt(s) required in tubular patterning is the use of a small-molecule inhibitor, IWP2. IWP2 inhibits Porcupine, an enzyme that is required for palmitoylation of Wnt proteins. Following treatment of LIM1863-Mph monolayer cultures with IWP2, recombinant Wnts, both individually and as groups will be reintroduced to the cells and their effect monitored. Insight into the functioning roles of Wnts and FZDs in CRC can offer novel avenues in treatments to target key events during tumor growth and progression.

57 DR HUI-LI WONG

IS THERE A ROLE FOR CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER PATIENTS WITH A POOR PERFORMANCE STATUS?

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Background: The management of patients with poor performance status (PS) remains challenging in the absence of data on optimal treatment. Here we assessed the treatment and outcomes of patients with metastatic colorectal cancer (mCRC) with poor Eastern Cooperative Oncology Group (ECOG) PS (>/= 2) in routine clinical care.

Methods: Analysis of patients prospectively entered onto the TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) database, a clinician-designed initiative to collect comprehensive data on consecutive patients with mCRC from sites across Australia. Data collection commenced in July 2009 and is ongoing at 14 participating public and private centres.

Results: Of the 864 patients entered, 161 (18.6%) had an ECOG PS >/= 2. In total, 95 (11.0%) were PS 2, 54 (6.3%) PS 3 and 12 (1.4%) PS 4. Chemotherapy was administered to 65 (68.4%) PS 2 and 17 (31.5%) PS 3 patients, with none of the PS 4 patients being treated. Overall, poor PS patients were significantly less likely to receive any chemotherapy compared to their good PS (PS 0-1) counterparts (51.6% versus 86.8%, p<0.0001) and, when chemotherapy was given, significantly less likely to receive combination chemotherapy (67.5% vs 81.1%, p=0.0057) or bevacizumab (31.3% vs 55.8%, p<0.0001).

Overall survival (OS) was reduced with declining PS, with medians of 28.7, 8.9, 3.5 and 0.8 months for PS 0-1, 2, 3 and 4 patients respectively (p<0.0001). Poor PS patients treated with chemotherapy had a better OS outcome (9.0 vs 3.5 months for untreated patients, p<0.0001). At one and two years, 24 (28.9%) and 7 (8.4%) treated poor PS patients were alive.

Conclusions: In routine practice many patients with a poor PS, particularly those that are PS 2, receive active treatment. Although overall survival for poor PS patients is poor, some patients appear to benefit from treatment. Further data analysis, particularly to define subsets that may benefit most from treatment, is planned as further sites around Australia contribute data to the project.

58 DR HUI-LI WONG

IMPACT OF DIABETES ON CLINICOPATHOLOGIC AND GENETIC FEATURES OF COLORECTAL CANCER FORMATION

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Background: Diabetes mellitus is reported to increase the risk of colorectal cancer (CRC) development and has been associated with poor tumour-specific outcomes. Here we assessed the impact of diabetes on the clinicopathologic features and tumour mutation profiles of CRC.
Methods: Analysis of a prospective series of patients diagnosed with CRC between January 2000 and December 2010. Fresh-frozen and formalin-fixed, paraffin-embedded tumour specimens were retrieved and genomic DNA extracted for analysis of microsatellite instability (MSI), CpG island methylator phenotype (CIMP) and mutations in BRAF, KRAS, PIK3CA, TP53 and APC genes. Propensity-score matching and logistic regression were used to estimate the association of diabetes with tumour molecular profile, controlling for age, sex, tumour stage, body mass index (BMI), smoking and socio-economic status.

Results: Of the 1348 patients assessed, 288 (21.4%) had a history of diabetes mellitus. Compared to patients without diabetes, diabetics were more likely to be older (age > 70 yrs: 56% vs 47%, p = 0.006), male (57% vs 47%, p = 0.002) and have a higher BMI (BMI > 25: 82% vs 65%, p < 0.0001). There were no statistically significant differences in tumour site, differentiation or lymphovascular invasion. Propensity scores were used to match 260 diabetic patients to an equal number of non-diabetics. In multivariate regression analysis, diabetes was associated with BRAF-mutated tumours (OR 2.81, 95% CI 1.16–7.59, p = 0.029) and showed a trend towards MSI-high tumours (OR 1.54, 95% CI 0.91–2.63, p = 0.110). There were no statistically significant differences in the remaining molecular characteristics for diabetic compared to non-diabetic patients.

Survival analysis is planned.

Conclusions: CRC patients with diabetes are older, more likely male and have higher BMI than non-diabetics. In this preliminary analysis, an association between diabetes and BRAF-mutant CRC was found, and may explain reported differences in outcomes for diabetic CRC patients.

59 DR SHU FEN WONG

PRIMARY TUMOR RESECTION IN METASTATIC COLORECTAL CANCER (mCRC): A PROSPECTIVE COHORT STUDY

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Background: The role of primary tumor resection in patients presenting with mCRC remains controversial. Previously reported survival benefits associated with primary tumor resection may not translate in the modern era of systemic therapies. We examined the impact of primary tumor resection on survival in a modern cohort of mCRC patients.

Methods: Patients were identified using a clinician-designed mCRC registry involving 15 participating Australian sites from mid 2009. Patients were excluded if planned for curative metastasectomy or had incomplete data. Univariate logistic regression and multivariate cox regression was utilized to identify significant associations between resection, clinical variables and survival outcomes.

Results: We identified 682 mCRC patients with median follow up 20 months. 40% (n = 275) had their primary in-situ. Rates of primary resection were higher for age > 70 years (OR 1.66, 95% CI [1.22 – 2.26], p = 0.001) and Charlson score ≥3 (OR 1.50, [1.10 – 2.06], p = 0.011). Lower resection rates were observed for rectal v colon primary (OR 0.39 [0.28 – 0.55], p = 0.001), liver metastases (OR 0.59 [0.42 – 0.82], p = 0.002) and ECOG 2-4 (OR 0.64 [0.45 – 0.92], p = 0.015). There was a significant survival advantage for pts with primary tumor resection (median OS 21.3 vs 16.8 months; HR 0.63, p < 0.001), even when adjusting for known prognostic factors in a multivariate analysis (HR 0.56 [0.44 – 0.72] p < 0.001). Multivariate analyses also demonstrated that age > 70 years (HR 1.32 [1.03 – 1.71], p = 0.031) and ECOG ≥ 2 (HR 3.17 [2.43 – 4.15], p < 0.001) were significantly associated with poorer outcomes; whereas chemotherapy use (HR 0.61 [0.45 – 0.84], p = 0.002), bevacizumab use (HR 0.68 [0.52 – 0.89], p = 0.005) and rectal primary (HR 0.69 [0.53 – 0.91], p = 0.009) predicted improved survival.

Conclusions: Our study suggests that primary tumor resection is associated with significant survival advantages for mCRC patients in the modern era of systemic therapies. The 40% of primary cancers in-situ is higher than previous mCRC studies and suggests a tendency for non-operative intervention in Australia. Further analysis aimed at examining the impact of other confounding variables such as tumor burden is ongoing and will be presented.

60 MS LISA CIABOTTI

PLANNING A BIG WEEKEND – OPTIMISING WEEKEND DISCHARGE RATES FOR MEDICAL PATIENTS

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Background: An organisation wide project ‘Optimising the Medical Patient Journey’ identified a decrease in discharges across the weekend.
Aim: To determine why fewer medical patients are discharged from the Royal Melbourne Hospital on weekends, compared to weekdays, and develop recommendations for methods of improvement.

Method: An audit of 102 medical inpatients was undertaken to identify potential weekend discharges, assess the presence of discharge planning and determine barriers. Forty five staff responded to a survey regarding opinions on enablers and barriers to weekend discharge. A literature review and benchmarking were completed to support development of recommendations.

Results: Baseline data revealed that 15% to 20% of discharges occur each day Monday to Friday, 8% on Saturdays and 4% on Sundays. Seventy-nine patients met inclusion criteria with discharge plans seen in 34 (43%). Six patients were discharged on the weekend, 27 (37%) of the remaining 73 were classified as potential weekend discharges with the most common barriers identified as awaiting medical and/or allied health review. Staff recognised lack of planning, poor processes and poor communication as barriers to discharge.

Conclusion: Suggested improvement strategies aim to target the deficiencies in patient assessment, discharge planning and communication. The development and implementation of a seven-day service model has a high potential to optimise weekend discharge rates.

MAXIMISING MEMORY: A REVIEW OF AN EDUCATION AND SELF MANAGEMENT GROUP PROGRAM FOR PEOPLE LIVING IN THE COMMUNITY WITH MEMORY DIFFICULTIES

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Background: Following international trends, Australia’s population is ageing. Consequently, the number of older people living with memory difficulties is rising. Group programs focusing on early intervention memory rehabilitation and self management for this population have not been common place in our community. Subsequently, an education and self management group was developed by the Occupational Therapy and Speech Pathology departments within the Community Therapy Service at Royal Melbourne Hospital.

Aims: To implement an evidence-based multidisciplinary memory self management group therapy program for older persons with mild memory difficulties and their carers. In addition, to evaluate its effectiveness as a service delivery model in a community setting.

Method: Patients with self reported memory concerns and or mild memory problems were invited to participate in a 6 week education and self management maximising memory program along with their carers. An action research model was used to evaluate the effectiveness of the program. Pre and post group data from 8 patients who participated in the memory group was collated, using a memory Self Efficacy Questionnaire. Paired t-tests were used to compare pre and post group changes in self efficacy with significance at p < 0.05. Further, a program evaluation was completed by the patients and their carers post group. Qualitative analysis of this feedback was obtained to determine what participants found helpful, not helpful and suggestions for improvement.

Results: Results indicated that patients participating in a 6 week maximising memory self management program demonstrated significant improvements in self rated efficacy in relation to perceived emotional impact of memory deficits and increased strategy use to manage their memory complaints. Overall, patients and their carers reported good satisfaction with the memory group with a 3 out of 4 rating.

Conclusion: This program has been found to be an effective method to empower older adults living in the community with the ability to manage cognitive decline and understand memory loss.

MALNUTRITION RISK IN AGED PERSONS MENTAL HEALTH: DEVELOPMENT OF A NUTRITION SCREENING TOOL

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Background: Malnutrition is common amongst the elderly and present in up to 55% of all geriatric patients admitted to healthcare settings. Previous studies have determined these rates are higher for those with mental health disorders. Malnutrition leads to increased length of stays, poorer health outcomes and increased healthcare costs. Early identification of malnutrition and nutrition interventions can improve outcomes. Physical assessment and monitoring of patients in mental health facilities is often sub-optimal with clinicians regularly focusing primarily on their presenting psychiatric issues and overlooking the nutritional status of a patient. Regular malnutrition screening therefore rarely occurs in such units. Malnutrition screening tools recommended for current general use have not been validated for elderly patients with mental health disorders. The lack of current literature supports the development of a validated malnutrition screening tool specific for Aged Persons Mental Health (APMH). This project
aims to determine current incidence of and practices related to malnutrition of patients admitted to APMH units at Melbourne Health.

Methods: An audit of the current prevalence of malnutrition within APMH inpatient units was conducted using the Subjective Global Assessment tool (SGA). Each patient was also screened for their malnutrition risk using three common screening tools (MNA, MUST and the MST). An audit of current food service practices and wastage as well as nutritional knowledge staff surveys were also undertaken.

Results: Thirty-eight inpatients at Sunshine, Broadmeadows and Bundoora APMH units were included in this audit. Overall 42% of patients were malnourished as assessed by SGA. The nutrition risk screening showed between 15% and 32% of patients to be at risk of malnutrition, depending on the tool used. However at admission the risk of malnutrition was as high as 82%.

Conclusion: Elderly patients with mental health disorders have a high prevalence of malnutrition and there is a clear need for the development and implementation of a validated nutrition screening tool. Processes were undertaken to develop appropriate tools for inpatient and residential care facilities. The project is currently in the stage of validating the tool and we hope to obtain results regarding the effectiveness of the tool’s implementation in the near future. The implementation of this tool has been supported by strategies such as the development of guidelines and staff education sessions.

63 DR AARON ROBINSON

CALCIFIC UREMIC ARTERIOLOPATHY IN A PATIENT WITH CHRONIC PLAQUE PSORIASIS- COULD TNF ALPHA INHIBITION MODIFY DISEASE PROGRESSION?

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Calcific uremic arteriolopathy (CUA, previously named calciphylaxis) is a serious disorder involving a complex cascade of pathology including dysregulation of calcium metabolism, systemic calcification of the arterioles, local inflammation, local thrombosis and occlusion, ischaemia and necrosis. This often leads to sepsis, and consequently CUA has a very high mortality rate, with a median survival of only 2.64 months after diagnosis.

We present the case of a 39 year old woman with CUA, on a background of end stage renal failure due to IgA nephropathy, hyperparathyroidism, ischaemic heart disease and chronic plaque psoriasis. This patient was on Etanercept (a TNF alpha inhibitor) for treatment of chronic plaque psoriasis, which was commenced four months before the first development of CUA lesions.

This patient died 22 months after initial presentation, as a result of a VF arrest, but was free of CUA lesions at this time. We hypothesise that treatment with Etanercept may have played a role in modifying disease progression in this patient.

Discussion is included of the pathogenesis of CUA, with reference to the possible points at which TNF alpha inhibition may play a role in modifying disease progression.

64 DR JOY YEE

ASSESSMENT OF CARDIOVASCULAR RISK IN BIOLOGICS PATIENTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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Psoriasis is a chronic inflammatory autoimmune disease associated with multiple co-morbidities including cardiovascular (CV) disease. Records from the Australasian Psoriasis Registry and Royal Melbourne Hospital were used to retrospectively assess the CV risk of biologics-naive patients using 10-year and 30-year Framingham Risk Score (FRS). These risk scores were compared with Psoriasis Area and Severity Index (PASI) scores from baseline to 35 weeks after treatment commencement. Results were compared across the four biologics currently used to treat psoriasis: adalimumab, ustekinumab, infliximab, and etanercept. The results suggested that this subset of patients is at high CV risk, reinforcing the importance of increased awareness for early intervention measures. The FRS should be used at baseline to predict risk, and to identify and educate at-risk patients, throughout the course of biologic treatment.

65 DR JOY YEE

THE EFFECT OF BIOLOGIC TREATMENT ON BODY-MASS INDEX (BMI) IN CHRONIC PLAQUE PSORIASIS PATIENTS

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Introduction: Obesity rates among individuals with psoriasis are higher than the general population (29% versus 18%)(1). Previous studies have shown that weight loss by obese patients improves psoriasis(2). This study evaluated correlation between changes in Body Mass Index (BMI) and psoriasis improvement in biologics patients, as measured by the Psoriasis Area and Severity Index (PASI).

Method: Demographic and clinical data were taken from the Australasian Psoriasis Registry and medical records from the Royal Melbourne Hospital. We compared the change in PASI score and change in BMI from baseline to 26-35 weeks in patients on adalimumab, etanercept, infliximab, and ustekinumab. Pearson correlation coefficient was used to measure the relationship between change in PASI score and change in BMI.

Results: Adalimumab patients showed a significant indirect correlation between BMI and PASI score from baseline to 26-35 weeks, while patients on ustekinumab showed a significant direct correlation between BMI and PASI from baseline to 26-35 weeks. Etanercept and infliximab patients did not show significant change in BMI during the study period.

Conclusion: These results suggest that adalimumab and ustekinumab significantly increase and decrease, respectively, the patient’s BMI while improving their psoriasis. The greater the PASI reduction, the greater the decrease in BMI (for ustekinumab) and the greater the increase in BMI (for adalimumab). As obesity is associated with multiple comorbidities, adalimumab patients may require nutritional and dietary support to counteract the tendency towards weight gain. The number of patients limits this study, and further exploration in a larger cohort would be of value.
fibrosis. The aim of the present study was to investigate the relationship between post contrast atrial T1 time and freedom from AF following pulmonary vein isolation (PVI).

Methods
112 patients with atrial fibrillation (63% paroxysmal AF; age 57.5±10.4 years; LA area 26.9±6.5cm²; LVEF 58.7±8.2%) underwent CMR with a 1.5T scanner prior to PVI and post contrast atrial T1 relaxation time was determined. Freedom from AF post ablation was documented by clinical review and 7 Day Holter monitoring at 6 monthly intervals.

Results
At a mean follow up of 12±5 months, 83 of 112 (74%) patients were in sinus rhythm off antiarrhythmic medication. In those with recurrent AF, the atrial post contrast T1 time was significantly shorter (215.6±32.4ms vs. 244.6±42.1ms; p=0.001). Univariate predictors of AF recurrence included post contrast atrial T1 time (p=0.003) and AF group (paroxysmal vs. persistent, p=0.019). Following multivariate analysis post contrast atrial T1 time was the only independent predictor of AF recurrence (p=0.006). Freedom from AF was present in 96% with a post contrast atrial T1 time >260ms vs. 68% in patients with atrial T1 < 260ms (p = 0.01).

Conclusions
CMR atrial T1 mapping provides a non-invasive measure of atrial structural remodelling. A shorter post contrast atrial T1 time is associated with increased AF recurrence following pulmonary vein isolation which may have implications for patient selection and ablation strategies.

DIFFUSE VENTRICULAR FIBROSIS MEASURED BY T1 MAPPING ON CARDIAC MRI PREDICTS SUCCESS OF ATRIAL FIBRILLATION ABLATION

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Introduction
Atrial fibrillation (AF) may be associated with varying degrees of cardiomyopathy. Cardiac magnetic resonance (CMR) imaging may demonstrate two patterns of ventricular fibrosis: (1) focal scar with discrete delayed enhancement or (2) diffuse fibrosis by contrast enhanced T1 mapping sequences. The aim of the present study was to investigate the relationship between ventricular post contrast T1 time and freedom from AF following pulmonary vein isolation (PVI).

Methods
94 patients with symptomatic AF (65% paroxysmal AF; age 57.5±10.5 years; LA area 26.5±6.7cm²; LVEF 58.4±8.4%; hypertension 35%) underwent CMR prior to PVI to determine post contrast ventricular T1 time. Baseline characteristics and procedural details were recorded. Follow up included clinical review and 7 Day Holter monitors at 6 monthly intervals.

Results
At a mean follow up of 12±5 months, 25 patients (27%) had recurrent AF post ablation. Post contrast ventricular T1 time was significantly shorter in patients with recurrent AF (360.6±67.5ms vs. 418.9±93.4ms in patients without AF recurrence; p=0.005). Univariate predictors of AF recurrence included post contrast ventricular T1 time (p=0.012) and AF group (paroxysmal vs. persistent, p=0.015). On multivariate analysis post contrast ventricular T1 time (p=0.030) and AF group (p=0.040) remained as independent predictors. Freedom from AF was present in 100% of patients with a post contrast ventricular T1 time >480ms vs. 68% in patients with post contrast ventricular T1 <480ms (p=0.015).

Conclusions
Reduced post contrast ventricular T1 relaxation time on CMR, consistent with diffuse ventricular fibrosis is associated with a reduction in freedom from AF post catheter ablation.

A MINIMAL OR MAXIMAL ABLATION STRATEGY TO ACHIEVE PULMONARY VEIN ISOLATION FOR PAROXYSMAL ATRIAL FIBRILLATION: ACUTE OUTCOMES IN A PROSPECTIVE MULTI-CENTRE RANDOMISED CONTROLLED TRIAL (THE MINIMAX STUDY)

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Introduction: Pulmonary vein (PV) reconnection is the Achilles heel of PVI isolation for atrial fibrillation. Antral PVI may include ablation along the intervenous ridge (IVR) to achieve individual PVI however whether this impacts on clinical outcomes is undetermined.
Methods: We performed a randomized multicenter international study to compare circumferential antral PVI alone (minimal) versus (2) circumferential antral PVI with IVR ablation to achieve individual PV isolation (maximal).

Results (see table)

166 patients with paroxysmal AF were randomized to a minimal or maximal ablation strategy to achieve CPVI. RF ablation time was longer in the maximal group with no significant difference in procedural or fluoroscopy times or acute PV reconnection. In the minimal group, 41% required ablation on the IVR to achieve PVI which was associated with a significant increase in acute PV reconnection (53%) compared with minimal group without IVR ablation (26%, p=0.01). Single procedure success off antiarrhythmic drugs did not differ between groups by an intention to treat analysis at mean follow up of 10±5 months (freedom from AF 78% in the minimal vs. 75% in the maximal group; p = 0.79).

Conclusion: Despite dedicated attempts to perform antral ablation, 41% require ablation on the intervenous ridge to achieve PVI which was associated with an increase in acute PV reconnection. However there was no significant difference in freedom from AF between PVI ablation strategies.

70 DR ALEX MCLELLAN

PULMONARY VEIN ISOLATION REQUIRING ABLATION ON THE INTERVENOUS RIDGE TO ACHIEVE ELECTRICAL DISCONNECTION: IMPACT ON ACUTE AND LONG TERM OUTCOME

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Introduction: Pulmonary vein isolation is the cornerstone for AF ablation strategies. Despite apparently complete encirclement of the pulmonary veins ablation “inside the circle” is required in a significant proportion of patients however the impact on clinical outcome is yet to be determined.

Methods and Results: 82 patients (Age 59±19 years, 60% male, hypertension 58%, LA size 26±7cm², LVEF 59±6%) underwent pulmonary venous antral ablation. Focal ablation on the intervenous ridge (IVR) was permissible only after completion of encircling ablation and repositioning of the circular mapping catheter confirmed the site of breakthrough originated from the IVR. Freedom from AF was documented by 7day Holter monitoring at 6monthly intervals.

35 (42%) required ablation on the IVR to achieve PVI. There were no differences in baseline or procedural characteristics, apart from longer RF ablation time in patients requiring IVR ablation. In patients with IVR ablation acute PV reconnection was significantly increased (53% vs. 26% in patients without IVR ablation; p=0.01). At follow up of 10±5 months there was a trend to reduction in freedom from AF in patients requiring IVR ablation (69% vs. 85% in patients not requiring IVR ablation; p=0.07).

Conclusions: Ablation on the intervenous ridge is required in a significant proportion of patients to achieve pulmonary vein isolation despite apparently complete antral encirclement. Intervenous ridge ablation was associated with an increase in acute PV reconnection with a trend to increased AF recurrence.

71 MR OLIVER SAYKAO

SPIROMETRY SHOULD BE PERFORMED PRIOR TO EVH REFERRAL

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Introduction: Eucapnic Voluntary Hyperventilation (EVH) is an expensive surrogate test for exercise induced bronchospasm. Baseline lung function is usually not performed before referral for EVH. The aim of this study was to investigate whether baseline spirometry could be useful in predicting a positive EVH result.

Method: Forty-four patients, 20 males, 24 females, (mean = 18 ± 8 years) were referred to the Respiratory Laboratory at the Royal Melbourne Hospital to perform a six minute single-dose EVH challenge test. Pre EVH and post EVH spirometry was recorded including FEV1, FVC and FER. Sustained reductions in FEV1 of ≥10% post EVH constituted a positive result indicative of Exercise-Induced Bronchoconstriction (EIB).

Results: 22 subjects (50%) demonstrated a positive response to the EVH challenge test. Receiver Operating Characteristic (ROC) curve analysis showed that the optimal FER cut-off point for identifying positive responses to the EVH challenge test was 82.5% with sensitivity = 0.82 and specificity = 0.91. Subjects who reacted positively showed a reduced baseline mean FER of 76.5% compared to the negative group (89.8%) p< 0.01. Fifty percent of the responders had baseline FER < 76%, where as only one (4.5%) of the non responders had this FER.

Conclusion: (i) Baseline spirometry with bronchodilator response is recommended before embarking on EVH challenge testing. (ii) Baseline FER below 76% is likely to be predictive of a positive EVH response.
IS ELECTROGRAM MORPHOLOGY & LESION SIZE PREDICTIVE OF CATHETER-TISSUE CONTACT FORCE DURING EPICARDIAL RF ABLATION IN AN OVINE MODEL

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Background: Contact force (CF) during radiofrequency ablation (RFA) is important for adequate lesion formation with limited data on epicardial RFA & CF. We evaluated epicardial electrogram (EGM) amplitude & lesion volume to determine predictive value for real-time CF using irrigated RFA in an ovine model.

Methods: In 12 sheep a 7F irrigated RFA catheter with CF sensor was introduced via a small pericardial incision onto & in parallel with ventricular epicardium. RFA (30 watts/30 sec duration) with constant CF was applied at 5g, 10g, 20g, 40g & 70g over left & right ventricular (LV/RV) myocardium. Baseline & post-RFA EGM amplitude plus lesion volume were correlated with actual CF applied.

Results: Increasing lesion volume correlated with higher CF with volume doubling between 5g & 40g of applied CF (r²=0.61, p<0.001). Largest LV lesions were not transmural due to significant baseline wall thickness (mean LV 15.5±3.2mm vs. mean RV 5.6±1.0mm). RV transmural lesions were frequently seen at 70g applications & occasionally at CF 40g. Baseline EGM amplitude & pre-RFA CF correlation was moderately-poor (r=0.24, p=0.008). Sensitivity & specificity for pre-RFA EGM amplitude to predict CF>20g were 41% & 86% respectively. Increasing EGM amplitude at higher CF trended towards significance (p=0.052). Lesion volume correlated at low (<25%) & moderate (25%-75%) EGM amplitude change (p=0.041) but not with >75% change (p=0.15). EGM amplitude change was not significantly different with increasing CF (p=0.448).

Conclusion: Epicardial lesion volume is strongly related to increasing CF. EGM amplitude has only modest correlation with CF demonstrating its limited value in predicting real-time CF during epicardial RFA in this model.

HIGH COSTS DRUGS - TAKING POSITIVE ACTION FOR TIMELY APPROVALS

DWYER J
The Royal Melbourne Hospital

Aim: To describe the benefits of a new approval process for high cost drugs at a large tertiary teaching hospital after a year of implementation

Background: The previous Individual Patient Usage (IPU) approval process involved medical staff telephoning Drugs and Therapeutic Committee (DTC) members for approval of high cost drugs (>-$1000/course), submitting an application to DTC monthly meeting and final review by Therapeutic Review Group monthly (consisting of Divisional Medical Directors).

Concerns raised regarding existing process included:

- contacting DTC members was too onerous;
- overall process was not timely for clinical decision making;
- when DTC members were not available the decision rested with pharmacy;
- Divisional Director decision-making in the absence of sufficient clinical information.

In 2011, 121 applications were approved totalling $363,000; with 32 extensions granted to pre-existing approvals totalling $216,000.

The Change: In 2011, the IPU process was amended so that applications are sent to DTC secretary and interim approval is given unless considered high cost. High cost (>-$1,000) applications are e-mailed to DTC medical members; if 4 medical members approve, then this is sent to the Divisional Medical Director for approval. Applications are subsequently tabled at monthly meetings.

Survey Methods: A online survey tool was used to assess the opinions of 3 groups of users of the high-cost DTC IPU approval process: • All pharmacists; • Medical members of the DTC; • Service Directors

Questions were asked to each 3 groups about:

- General understanding of the process;
- Timeliness of approval;
- Clinical justification required;
- Financial justification required;
- Consideration of patient care;
- Suggestions to improve the process

Results: There were 37 high-cost IPU applications received for approval between June and August 2012.

Conclusion: Change of IPU process using email has improved patient approval process, increased medical staff engagement, and facilitated more timely drug administration. The median time to approval for high cost IPU applications was 3 days. This is an improvement on having to wait for two monthly meetings prior to approval.
Further education on the process for high-cost urgent applications, and applications out of business hours was requested.

**74 MS MARLENA KLAIC**

UNDERSTANDING ALLIED HEALTH PROFESSIONALS’ USE OF RESEARCH EVIDENCE USING THE THEORY OF PLANNED BEHAVIOUR.

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Background: There is a significant body of research which suggests that allied health professionals agree with the philosophy of evidence based practice (EBP), and believe that research evidence can improve patient care. However, actual implementation of research findings into clinical practice is poor with numerous barriers cited. The aim of this study was to identify and describe the factors that influence allied health professionals implementation of research evidence in clinical practice, using the theory of planned behavior.

Methods: Allied health professionals from dietetics/nutrition, occupational therapy, physiotherapy, psychology, social work, speech pathology and other were invited to complete an on-line survey (n=496). The survey measured attitudes, confidence and skills towards EBP and participation in EBP activities. Results were analysed using the theory of planned behaviour.

Results: A total of 288 allied health clinicians completed the survey, indicating a response rate of 58%. The study revealed that allied health clinicians have a positive attitude towards EBP (behavioural belief) and believe they should be implementing research evidence into clinical practice (subjective norms). However, allied health clinicians from all disciplines reported difficulties in most EBP behaviours, such as appraising research evidence (perceived behavioural control). The theory of planned behaviour proposes that perceived behavioural control is an important determinant of a clinician’s likelihood to change his/her behavior.

Conclusion: This study demonstrates that the theory of planned behaviour can provide a framework in which to understand allied health clinicians’ current experience of EBP. Strategies to enhance allied health clinicians’ use of research evidence in clinical practice should focus on perceived behavioural control.

**75 MISS ANNA KULMAN**

TIMELINESS AND ACCURACY OF PRESCRIPTIONS; REACTING TO BARRIERS AGAINST EFFICIENT DISCHARGE PROCESSES

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Melbourne Health

Aim: To identify common deficiencies in general medical discharge prescription processes at a tertiary hospital.

Background: Anecdotal reports of same day discharge prescriptions provided to clinical pharmacists after the 3pm discharge planning meeting suggest an impact on timely discharge and patient care.

Method: Using lean six-sigma methodology, patients were identified prospectively over five days at point of discharge on two, thirty-bed general medical wards. Data was collected regarding time prescriptions were received and clinically screened by the pharmacist and compared to the time and date of the discharge. Prescriptions were analysed for the number and type of discrepancies identified at screening and whether these were classified as true discrepancies or as previously undocumented, intentional changes in therapy.

Results: Fifty-six patients were identified and included for analysis. Following screening, these prescriptions comprised 873 medications.

Timeliness: Of 56 prescriptions received, 42 (75%) prescriptions were received on the day of discharge. Three (5%) prescriptions were received after 3pm for same day discharge. Fourteen (29%) patients were discharged before 10am from the ward, with four (29%) of these having prescriptions written earlier than day of discharge.

Discrepancies: Of 56 prescriptions received, 50 (89%) contained discrepancies, with 551 discrepancies identified in total. 414 (75%) discrepancies were omitted PBS requirements. Of the remaining discrepancies, omitted medications and inappropriate dosing were most common. Twenty-seven (5%) identified discrepancies were intentional changes in therapy, not communicated or documented by the prescriber.

Conclusion: Two common issues were identified - the number of prescriptions received on the day of discharge and the number of prescriptions requiring pharmacist intervention. The anecdotal evidence of prescriptions being received after 3pm was not confirmed from the data. A multi-disciplinary solutions workshop has been proposed to improve the discharge planning and accuracy of prescriptions for medical patients and release of pharmacist time to patient care.
IDENTIFYING PATIENT OUTCOMES USEFUL TO MEASURE THE QUALITY OF INTER-PROFESSIONAL HANDOVER IN THE POST ANAESTHETIC CARE UNIT (PACU).

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Background: Effective handover communication makes a significant contribution to the delivery of safe patient care. The busy, complex PACU care environment has high risk for handover miscommunication. Patient safety literature recognises poor quality handover as a major problem, however, patient outcomes directly impacted by inter-professional handover in the PACU have not been identified.

Aim: Identify potential indicators useful to measure patient care outcomes related to the quality of inter-professional handover between the Anaesthetist and the PACU Nurse. The research questions are:

• What is the trajectory of patient care in the PACU?
• What are possible indicators to measure patient outcomes that are sensitive to the quality of inter-professional handover in the PACU?

Methods: An exploratory mixed-methods approach using naturalistic inquiry was utilized. Observational data were collected across three hospital sites; details of the anaesthetist to nurse handover and all patient care activities during the patients PACU stay were recorded. A specifically designed “tap form” using iPad technology was used to collect both quantitative and qualitative data in real time. 31 ‘patient journeys’ across three sites was sufficient to reach data saturation. Data were analysed using quantitative and qualitative methods.

Results: Data analysis is ongoing. Quantitative examination of the frequency, duration and sequence of common PACU care activities revealed observations (haemodynamic assessment, vital signs), pain management (analgesic administration) and communication were the most common care activities undertaken in the PACU. Patterns in the data were also used to generate patient maps of the trajectory of care taking place in the PACU. Patient care activities, their frequency and duration will be used to identify patterns and links to possible patient outcome indicators sensitive to the quality of inter-professional handover communication into the PACU.

Conclusion: Patient’s pain on discharge from PACU and timely escalation of care to respond to deterioration were identified as possible indicators sensitive to the quality of inter-professional handover communication into the PACU. Nurse’s ability to perform these common PACU activities was often linked to handover communication on arrival in PACU. This research provides the foundation for future research to test the sensitivity of care indicators and measure quality improvement of inter-professional handover into the PACU.

THE COST-BENEFIT OF USING SOFT SILICONE MULTI-LAYERED FOAM DRESSINGS TO PREVENT SACRAL AND HEEL PRESSURE ULCERS IN TRAUMA AND CRITICALLY ILL PATIENTS: A WITHIN-TRIAL ANALYSIS

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1 The Royal Melbourne Hospital, 2 The University of Melbourne, 3 The Royal Park Hospital

Background: Pressure ulcers are resource intensive and expensive to treat. The focus of cost saving should be on pressure ulcer incidence reduction. Evidence has shown the effectiveness of soft silicone multi-layered foam dressings in pressure ulcer prevention. However, little is known about the cost-benefit of prophylactic dressings that reduce pressure ulcer incidences among critically ill patients in the emergency department and intensive care unit.

Methods: This cost study was based on a prospective randomised controlled trial of the efficacy of soft silicone multi-layered foam dressings in the prevention of sacral and heel pressure ulcers among critically ill patients in the Royal Melbourne Hospital. Eligible patients were randomly allocated into an intervention group with prophylactic dressings applied to the sacrum and heels in the emergency department and changed every three days in the intensive care unit, or into a control group with standard pressure ulcer prevention care provided during their emergency department and intensive care unit stay. All patients were assessed daily in the intensive care unit to determine the hospital acquired pressure ulcer incidence rates. The cost-benefit analysis was conducted from a healthcare sector’s perspective.

Results: 440 (control n=221; intervention n=219) patients were initially recruited into the trial. Excluding deaths, loss to follow-up and transfers to another ward or hospital, 313 (control n=152; intervention n=161) patients were included in the final analysis. The results showed a significant reduction of pressure ulcer incidence rates in the intervention group (p=0.001). The intervention cost was estimated to be AU$34.14 per person based on an intention to treat analysis, but this was offset by lower downstream costs associated with pressure ulcer treatment (AU$1103.52). Therefore, the average net cost of the intervention was lower than that of the control (AU$68.35 vs AU$144.56). The results are robust to examinations of uncertainty surrounding key variables.
Conclusion: We conclude that the use of soft silicone multi-layered foam dressings to prevent sacral and heel pressure ulcers among critically ill patients results in cost savings in the Royal Melbourne Hospital.

**DEVELOPING A CLINICAL EDUCATION AND SUPPORT PROGRAM (HAND THERAPY) FOR REMOTE BASED CLINICIANS**

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**Background:** Hand therapy is an ever growing profession, imperative to improving hand function following acute hand injury. Despite many injuries occurring in rural and regional areas, clinical knowledge and expertise is predominantly located in major cities or metropolitan areas. Generally, this requires patients to travel lengthy distances to receive specialist intervention, often increasing the financial and time burden on family and friends to provide transport to these appointments. To ensure we continue to achieve optimum outcomes for our patients, it is imperative that we as a profession increase the knowledge and clinical skills of remote based clinicians in relation to the management of these often complex conditions.

The aim of this travelling fellowship was to develop a framework for which a Clinical Education and Support Program for remote based clinicians with a specific focus on hand therapy could be established. This program aims to facilitate an increase in local care for patients with hand injuries, whilst not jeopardising clinical outcomes.

**Method:** Nineteen hand therapy centres across the United States of America, Canada and England were visited over an eleven week period. During the site visits, structured interviews were undertaken and relevant processes related to the management of remote based patients and clinician education were reviewed.

**Results:** Many of the hand therapy centres visited face similar challenges in regards to providing high level care and achieving optimum outcomes for patients based in rural and regional areas. Utilising a shared model of care will facilitate the transfer of care, whilst building remote based clinicians’ knowledge and skill and not jeopardizing patient outcomes.

**Conclusions:** Following completion of the travelling fellowship and consideration of the knowledge gained, a framework to guide a Clinical Education and Support Program has been established. It is recommended that a multi-faceted program include:

- Workshops or study days
- Clinical handbooks
- Online discussion and support forum
- Structured observational opportunities
- Shared-care model of health care

A more comprehensive program may also incorporate the following resources:

- Electronic learning modules
- Electronic mail out which may include condition specific information or therapist tips and tricks
- DVD or handbook of patient educational handouts

Utilising the outlined framework will facilitate the successful implementation of a comprehensive Clinical Education and Support Program specifically related to hand therapy. This will ultimately enable local care for patients with hand injuries without compromising outcomes. Furthermore, this framework could be adapted to other services provided within the tertiary setting of Melbourne Health.

**QUALITY OF CARE FOR THE PREVENTION OF CATHETER ASSOCIATED URINARY TRACT INFECTION (CAUTI).**

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**Background:** Urinary tract infections account for up to 40% of nosocomial infections and 80% of these are related to the presence of an indwelling urinary catheter. Numerous patient, device and device management factors increase risk of catheter associated urinary tract infection (CAUTI).

**Aim:** The primary aim of this study was to identify the prevalence of urinary catheter device use within Melbourne Health. Secondary aims were to determine practice patterns in relation to nurse sensitive indicators for the prevention of CAUTI, to identify the incidence of assessable indicators of CAUTI associated infection and to identify the frequency of diagnosed urinary tract infection in this setting at a single point in time.
Methods: A point prevalence survey of indwelling catheter use at the Royal Melbourne and Royal Park campus of Melbourne Health was undertaken over 2 days in January 2013. Results: There were 697 in-patients assessed during this survey, 68 (9.7%) of whom had an indwelling catheter. Of these patients 17.6% (n = 12) had a urine sample sent for culture that was positive for growth sensitive to a range of antimicrobials in 50% (n = 6) of cases. When infection was present there was insufficient evidence to demonstrate a relationship between the presence of indicators of infection and a positive culture. There were interesting trends in terms of nurse sensitive indicators evident in practice patterns at the time of the survey. Conclusion: Urinary catheter use was frequent and when CAUTI was suspected urinary cultures were often positive for growth. However, accepted indicators of infection although easy to identify were not indicative of this complication. Maintaining appropriate and adequate interventions for the prevention of CAUTI is complex. Practice patterns demonstrate room for improvement in relation to nurse sensitive indicators for the prevention of infection.

80  MRS BERNICE REDLEY

IMPROVING THE QUALITY OF INTER-PROFESSIONAL HANDOVER INTO THE RECOVERY ROOM

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Objectives: Building upon previous quality improvement research the aim of this research is to evaluate clinician uptake of three quality improvement tools to standardise inter-professional clinical handover processes for the transfer of care from the operating room to the PACU.

Methods: Prospective, naturalistic observations at three hospital sites, one public and two private, were used to examine handover processes at the transfer of patients care from the operating room into the PACU using an evidence based framework. Data were captured by trained clinician observers using an observation audit tool based on the 4 components of recommendations for a best practice handover process (COLD) from the anaesthetist to PACU nurse; connect the patient to monitoring devices (C), observe and respond to immediate patient safety (O), stop to listen to handover (L), and delegate responsibility using a checklist (D). Handover tools (ISOBAR to guide verbal content and a 10 point checklist) were used to evaluate the quality of verbal and documented information transfer respectively. The observation audit tool was tested for validity and reliability.

Results: Analysis of observation data from over 900 PACU ‘real time’ clinical handover events identified clinician behaviours that indicate consistent use of elements the improvement tools as well as gaps in clinical practice. High compliance with Connect and Observe behaviours were observed. At two sites where the tools were introduced, changes were most often noted in relation to clinician behaviours of ‘Listen’ (stop multi-tasking to listen to verbal handover) and ‘Delegation’ practices (questions to clarify information at handover, receiver indicating they are happy) were observed. The frequency of distractions and interruptions during handover and patient pain scores at discharge from PACU also decreased. Ongoing gaps in handover practices that may impact patient safety relate to patient identification checking (observed in <11% of handovers); communication of allergies (up to 24% missed); communication of vital signs; and an escalation plan to respond to clinical deterioration.

Conclusion: This study of PACU handover improvement tools in “real-world settings” has demonstrated the feasibility of clinicians using the tools to standardize handover practices and revealed factors critical for clinician adoption of the tools. Handover behaviours that reflect good practices safer clinical communication as well as practices that continue to pose risks to patient safety were identified and described to facilitate training. Understanding the ways and contexts in which clinicians work is essential to incorporate new handover solutions into routine practice to improve patient safety.
PATIENT SATISFACTION WITH A NURSE PRACTITIONER TIA CLINIC

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Background: Transient Ischaemic Attacks (TIA) are a warning sign for stroke. Urgent treatment is required to reduce stroke risk. Management generally occurs by specialist stroke services. Stroke Nurse Practitioners (SNP) can help meet increasing service demand. The Royal Melbourne Hospital has Australia’s first SNP, and has set up a SNP led clinic for assessment and management of TIA outpatients in an autonomous collaborative framework with the RMH Stroke Neurologists.

Aims: To evaluate patient satisfaction with care with the SNP led TIA outpatient clinic at Royal Melbourne Hospital (RMH).

Methods: An independent research officer recruited eligible patients (diagnosed with TIA; aged ≥18 years; Modified Rankin Scale score <4; English speaker) immediately following their clinic appointment. Satisfaction with care was assessed using quantitative (questions from the Australian Nurse Practitioner Study Research Toolkit) and qualitative (semi-structured interview) methods.

Results: To date, 24 patients have completed the satisfaction surveys (68% male; mean age 68 years). 79% had not heard of a SNP before. All reported satisfaction with the service (96% highly satisfied). All patients indicated the SNP spent enough time with them and listened to them carefully, and they would see a SNP again and would recommend a SNP to family and friends. Qualitative results indicate patients valued receiving detailed health information from the SNP in an understandable way in a friendly and relaxed environment.

Discussion: An SNP TIA clinic is feasible and associated with high levels of patient satisfaction. Challenges include current limitations in access to Medicare Benefits Scheme when working within a public hospital leading to NP practice inefficiencies.

COMPARING AGREEMENT BETWEEN MORTALITY AUDIT AND THE GLOBAL TRIGGER TOOL

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(3) Melbourne University
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(5) Monash University

OBJECTIVE: This clinical audit aimed to compare agreement between Mortality Audit (MA) and the Global Trigger Tool (GTT) for ascertainment of adverse events (AE).

METHODS: At Melbourne Health (MH) the MA and GTT are two AE surveillance systems involving patient record review:

- GTT involves structured screening of medical records by a trained nurse using defined ‘triggers’, with review by trained physicians. It has demonstrated high inter-rater reliability at MH, better identifying AE than Incident Reporting Systems in international studies.
- For MA, all deaths undergo structured screening and review by clinical department medical staff. A Quality of Care (QoC) issue has occurred when the MA reviewer identifies: an area of consideration, an area of concern, or an AE. Attributes of MA (e.g. inter-rater reliability) have not been tested, nor have comparisons with other methods been undertaken.

A random sample of deaths (n=20) that had undergone MA (10 with and 10 without QoC issues) were reviewed by the GTT team using usual methods but blinded to QoC status. Level of agreement about AEs was assessed between GTT and MA. Qualitative analysis of record statements about the deaths was undertaken.

RESULTS
- AEs were documented in 0/20 MA and 13/20 GTT (5/20 were considered by GTT team to have contributed to patient death)
- Area of concern/consideration (AC/C) was documented in 10/20 MA, of which 8/10 were classified as AE on GTT
- 10/20 MA had no AC/C, of which 5/10 GTT documented an AE
- Estimated Kappa statistic of 0.30 (95% CI: -0.10 to 0.70), indicates a ‘fair’ level of agreement between a QoC issue in the MA and AE on GTT

Qualitative analysis:
• Suboptimal classification of AE within MA with a strong focus on preventability even though this isn’t part of the accepted definition of an AE. 5/10 records noted ‘non-preventability’ and 1/10 ‘low preventability’.
• GTT identified 4 cases where end of life (EOL) discussion might have been recommended or recommended earlier than occurred.
• MA identified communication as an issue in 5/10 cases with AC/C.

CONCLUSION: There’s a low level of agreement between MA and GTT with regard to ascertainment of AE. Themes identified in MA (e.g. EOL discussions) could contribute to system improvement. For MA to provide a useful quality assurance and clinical educative role, further training of medical staff is required or a central MA surveillance system introduced to maximise utility for system improvement.

83 PROF PETER COLMAN

GLUCOMETRICS - AN APPROACH TO ANALYSING HOSPITAL WIDE DIABETES CARE

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BACKGROUND: There is increasing awareness of the morbidity and mortality associated with hyperglycaemia in hospital inpatients. The analysis of point of care blood glucose measurements (POC-BG) or ‘inpatient glucometrics’ has been suggested as an important measure of in-hospital glycaemic control.

OBJECTIVE: To examine the feasibility of utilizing glucometrics in patients at the Royal Melbourne Hospital as part of a hospital wide diabetes care improvement project.

METHODS: 14192 point of care blood glucose (POC-BG) measurements were extracted from 57 blood glucose meters on one day.

RESULTS: All inpatient units were represented: 72% blood glucose level (BGL) measurements were from general wards, 18% from ICU, 5% from psychiatry and 3% from operating theatres. There were also 328 measurements (2%) from outpatients. 43% of BGL measurements were taken between 8am and 5pm, 20% between 5pm and 10pm, 28% between 10pm and 6am and 9% in the early morning between 6am-8am. The mean BGL across all glucose measurements was 9.4 mmol/L with mean values ranging from 8.07 mmol/L (BGLs from outpatients) to 10.45 mmol/L (BGLs from oncology wards). 57.5% of all BGL measurements were within the recommended glycaemic target of 4-10 mmol/L. 6.6% of all measurements were in the hypoglycaemic (< 4 mmol/L) range, 24.2% in the mildly hyperglycaemic range (>10-15 mmol/L), 10% in the moderately hyperglycaemic range (>15-20) and 1.8% in the severely hyperglycaemic (>20 mmol/L) range. There was no difference observed in glycaemic control between weekdays and weekends.

CONCLUSION: Hyperglycaemia is common in hospital inpatients. Glycaemic control varies across wards and between inpatient and outpatient settings. Glucometric analysis is a method of capturing current in-hospital glycaemic control that may be used to assess the effectiveness of future intervention strategies.

84 PROF PETER COLMAN

AN AUDIT OF PSYCHOLOGICAL WELL-BEING IN ADULTS WITH TYPE 1 DIABETES ATTENDING TERTIARY DIABETES CLINICS IN MELBOURNE

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Aim: International studies have found that between 20-40% of people with type 1 diabetes (T1DM) experience poor psychological well-being. Routine monitoring of well-being is recommended in international guidelines but is not clinical practice in Australia. The aim of this audit was to examine the feasibility of monitoring psychological well-being and to assess the prevalence of diabetes-related distress and impaired well-being among adults with T1DM attending one of three tertiary, metropolitan diabetes clinics.

Method: Over a 12–week period, all clinic attendees were invited to complete a set of questionnaires in the waiting room prior to their consultation with an endocrinologist.

The Problem Areas In Diabetes (PAID) questionnaire and the WHO-5 Well-Being Index (WHO-5) were used to monitor diabetes-related distress and well-being respectively. Respondents were also asked to self-report diabetes treatment/complications, emotional problems, their personal agenda for the diabetes consultation and demographics. Completion time averaged 10-15 minutes.

Results: A total of 441 adults with T1DM participated (mean age 37±15yrs; range 18-80; 53% women).

The mean score (max score 100) for the PAID was 22.6±17.0 and for the WHO-5 was 57.4 ±21.3. No significant difference was observed between clinics: 12-20% reported severe diabetes related-distress (PAID score ≥40) and 30-
35% impaired well-being (WHO-5 score ≤ 50). Thirty five percent expressed the desire to talk to someone in their diabetes team about their feelings of living with diabetes.

Conclusion: This audit demonstrated the feasibility of monitoring psychological well-being at outpatient consultations. The prevalence of diabetes-related distress and impaired well-being were consistent with international reports. Adults with T1DM attending tertiary hospital clinics clearly expressed the desire to talk to a diabetes team member specifically about their experiences of living with diabetes. The next step is to translate these results into routine practice and develop interventions to improve psychological well-being among people with diabetes.

**PREVALENCE OF SELF-REPORTED SEVERE HYPOGLYCEMIA IN ADULTS WITH TYPE 1 DIABETES ATTENDING TERTIARY CLINICS IN MELBOURNE**

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The Australian Centre for Behavioural Research in Diabetes; Deakin University; AHP Research; Royal Melbourne Hospital; Baker IDI; St. Vincents Hospital

Aim: The aim of this study was to examine self-reported prevalence of severe hypoglycaemia (SH) in unselected adults with type 1 diabetes (T1DM) attending one of three tertiary, metropolitan diabetes clinics, and its association with psychological well-being.

Method: Over a 12-week period, all clinic attendees were invited to complete a questionnaire while awaiting their consultation with an endocrinologist. Questions asked about frequency of SH in the past 6 months, defined as ‘a hypo where you needed help/were unable to treat yourself’. Impaired awareness of hypoglycaemia (IAH) was assessed with the "Gold-score", a one-item 7-point scale with scores >4 indicating IAH. Two validated scales (PAID and WHO-5) measured diabetes-related distress and general psychological well-being respectively.

Results: In total, 441 adults with T1DM participated: mean±SD age 37±15 years; diabetes duration 18±12 years; HbA1c 7.9±1.3%. Over half (53%) were women, 25% used an insulin pump. Nineteen percent (N=79) experienced at least one SH in the past 6 months. A total of 195 episodes were reported by these 79 participants (mean 2.5 episodes/person); 10 people experienced 50% of the episodes. Twenty-one percent (N=93) had IAH. Compared with those who did not report SH, those who experienced SH had a longer diabetes duration (22.0±12.9 versus 17.6±11.7 years, p<0.01), were more likely to have IAH (3.6±1.6 versus 2.2±1.3, p<0.01), poorer well-being (49.7±21.5 versus 59.1±20.8, p<0.01) and higher diabetes-related distress (28.4±19.1 versus 21.2±16.3, p<0.01). There was no association with age, gender, insulin treatment (injections/pump) or HbA1c.

Conclusion: In this group of adults with T1DM, one in four reported at least one SH event in the past six months, with a small number experiencing the majority of the episodes. These results underline the need to relax glycaemic targets in this high risk group and/or to implement educational interventions to restore hypoglycaemia awareness and reduce SH.

**DOUBLING OF DIABETES PREVALENCE IN HOSPITAL INPATIENTS FROM 1996 - 2012**

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Royal Melbourne Hospital

Background: Point prevalence studies of diabetes were performed at Royal Melbourne Hospital (RMH) in 1996, 2000, and 2008. These documented a hospital population enriched for diabetes, with prevalence among inpatients of 15, 23, and 27% respectively.1,2,3

Aims: To determine the current prevalence of diabetes among RMH inpatients as well as the admission indication, length of stay, and glycaemia in diabetes inpatients.

Methods: A point prevalence study of RMH inpatients (n=310) was conducted on May 2, 2012 (ED and ICU excluded). Demographic and anthropometric data were obtained by patient interview and measurement, admission diagnosis and classification of diabetes status from documentation in the clinical record, and capillary blood glucose level (BGL) data from the current observation chart.

Results: The mean age was 63.4 years (58% male). Diabetes was documented in 93 (30%) inpatients. This was significantly higher than previous RMH surveys, and double the prevalence reported in 1996 (p<0.001) (Figure 1). Mean BMI was 27.5 kg/m2 in non-diabetes versus 30.0 kg/m2 in diabetes inpatients with 83 (89%) having type 2 diabetes. Of the diabetes patients, 36 (39%) were admitted for a problem directly related to diabetes (acute coronary syndrome, stroke, diabetic foot complication, or heart failure secondary to known/presumed ischaemic cardiomyopathy). Fifty (54%) diabetes inpatients were on insulin therapy and 16 (32%) of these had documented hypoglycaemia (BGL < 3.5mmol/L). Median length of stay was 9 days for patients without and 11 days for patients with diabetes, p=0.028 (15 days for insulin-treated and 7 days for non-insulin-treated diabetes).
Conclusion: One in three hospital inpatients had diabetes, with prevalence doubling in the last 15 years. Inpatients with insulin-requiring diabetes have greater length of stay and are at risk of hypoglycaemia. Recognition of the increasing frequency of diabetes in inpatients has major implications for hospital service and care planning, locally and nationally.

87 DR SPIROS FOURLANOS

INPATIENT DIABETES AUDIT IDENTIFIES FREQUENT DIABETES MEDICATION ERRORS AND SUBOPTIMAL GLYCAEMIA

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Background: Diabetes is increasing in hospitalized patients (1) and its management is complex with suboptimal glucose control, medication errors and patient complaints being common. Inpatient diabetes is associated with adverse outcomes including life threatening metabolic complications (diabetic ketoacidosis, hyper- and hypoglycaemia), infection, increased length of stay and increased mortality.

Aim: To assess inpatient diabetes management specifically in relation to diabetes medication errors and resultant glucose control.

Methods: We retrospectively audited the medical records of 85 inpatients of the Royal Melbourne Hospital during September 2011. We examined the patients’ medical history including progress notes, glycaemic records and medication chart aiming to assess the adequacy of oral hypoglycaemic and insulin diabetes medication prescription and administration in addition to frequency of adverse effects including hypoglycemia (capillary blood glucose level (BGL) <4mmol/l), hyperglycaemia (BGL>10mmol/l).

Results: The 85 consecutive inpatients with diabetes (mean age 75 ± 24 years, 51% males) were admitted, under multiple medical and surgical units for an average 10.5 day length of stay. Only 9.4% of patients were reviewed by the inpatient Diabetes and Endocrinology service. Fifty-eight (68%) inpatients had at least one error associated with the prescription or administration of an oral hypoglycaemic medication and eighteen (21%) at least one error in the prescription or administration of insulin (Table 1). Sixty (71%) inpatients did not have optimal BGL monitoring (QID testing pre-meals and nocte). Forty-five (53%) inpatients experienced a peak BGL of >14 mmol/l with 26% experiencing a peak BGL of >18mmol/l. Twenty inpatients (23.5%) experienced at least one episode of hypoglycaemia during the admission.

Conclusions: The management of diabetes medications in hospital inpatients is suboptimal and a contributor to hyper and hypoglycaemia. This audit identifies areas for improvement in diabetes medication prescription and administration to enhance patient safety.

88 DR SPIROS FOURLANOS

PERIOPERATIVE DIABETES AUDIT IDENTIFIES INCONSISTENT PRACTICE AND SUBOPTIMAL GLYCAEMIA

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Background: Diabetes affects approximately 30% of hospitalised patients (1). Inpatient diabetes management is complex with suboptimal glucose control and medication errors being common (2). Perioperative diabetes management is complicated by reduced oral intake and increased metabolic demands. Adverse outcomes include life-threatening metabolic complications (diabetic ketoacidosis – DKA, Hyperosmolar nonketotic coma - HONK, hyper- and hypoglycaemia), infection (3), increased length of stay and increased morbidity and mortality (4).

Aim: To assess perioperative diabetes management specifically in relation to diabetes medication errors and resultant glucose control.

Methods: We retrospectively audited 104 consecutive inpatients with diabetes (mean age 69, 54% male, 95% type 2 diabetes, 42% insulin-requiring) who underwent procedures (majority orthopaedic, vascular or interventional cardiology) at the Royal Melbourne Hospital. We examined patients’ medical records (progress notes, glycaemic records and medication charts) in relation to the immediate preoperative diabetes management (12 hours pre and post procedure) including the adequacy of glycaemic monitoring (2 hourly preop and 4 hourly postop), oral hypoglycaemic medication and insulin management and frequency of adverse events (hypoglycaemia: capillary blood glucose level [BGL] <4mmol/l, hyperglycaemia: BGL>11mmol/l).

Results: 26% of inpatients had written perioperative diabetes management plans. 80% of patients had oral hypoglycaemic medications appropriately withheld. Preoperative BGLs were monitored 2 hourly in 39% of inpatients and postoperative BGLs monitored 4 hourly in 38% of patients. Hypoglycaemia (BGL<4) was identified in 10% of patients; 55% of BGLs were within target (4–10 mmol/l) with a significant trend to worsening glycaemia in the later
postoperative period. There were no episodes of DKA or HONK. A minority of patients (12%) received care from the Endocrinology team.

Conclusions: The perioperative management of inpatient diabetes did not always follow established best practice. This audit identifies perioperative care as a major issue; given the numbers of hospital inpatients with diabetes a comprehensive inpatient diabetes service accompanied by guidelines may promote consistency and improve outcomes in the perioperative management of diabetes.

**89  DR SARAH PRICE**

**OBESITY IS ASSOCIATED WITH RETINOPATHY AND MACROVASCULAR DISEASE IN TYPE 1 DIABETES.**

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Excessive body weight is increasingly seen in type 1 diabetes but its impact is debated. To address this uncertainty, we aimed to determine the association between excess body weight and the macro-- and microvascular complications of type 1 diabetes. We identified 501 adults with type 1 diabetes attending an Australian hospital clinic and extracted their clinical and biochemical data from our patient management database. In both men and women, obesity (BMI>30kg/m2) was the predominant risk factor for retinopathy and cardiovascular disease despite similar HbA1c and increased use of cardioprotective drugs compared to non--obese patients. Obesity was associated with albuminuria in women, but not renal impairment or neuropathy in either sex. We conclude that obesity in type 1 diabetes may promote retinopathy and macrovascular disease. Future trials to determine the effect of weight loss on type 1 diabetes in obese people are needed.

**90  DR GEETHA RATHNAYAKE**

**INSULIN LIKE GROWTH FACTOR-1 ASSAY BIAS CAUSED HIGHER RATE OF Discordant GROWTH HORMONE DURING ORAL GLUCOSE SUPPRESSION**

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Context: Serum Insulin like Growth Factor-1 (IGF-1) is critical in evaluation of Growth Hormone (GH) excess or deficiency. Several laboratories in Australia received clinical feedback regarding elevated IGF-1 results which were discordant with clinical presentations. Further investigations revealed a positive bias of the Siemens Immulite IGF-1 assay since 2010.

Objective: To determine whether there was an upward drift of Immulite 2000 IGF-1 assay due to lot-to-lot reagent variability and whether there was a higher number of clinically discordant elevated IGF-1 results.

Design, Setting, Subjects, and Methods: We retrospectively extracted all IGF-1 and oral glucose tolerance test (OGTT) GH nadir (GHn) results from Melbourne Health Pathology over a 6 year period (1/1/2006 to 31/8/2012). A review of clinical record and MRI pituitary reports was conducted. All high IGF-1 results were defined by the age specific reference ranges provided by the manufacturer. Patients on somatostatin analogues, dopamine agonists, pegvisomant or had pituitary surgery/irradiation within 6 months of the test result were excluded. Elevated IGF-1 levels with available GHn were separated into 2 time periods: 2006-2009 and 2011-2012. A GHn of < 0.4 ug/L was considered adequate suppression. Normal or low IGF-1 levels in patients without acromegaly who had tests performed in 2008-09 and 2011-12 were compared using paired t-test.

Results: Of 548 elevated IGF-1 results performed over the 6 year period, 27 GHn were available. The proportion of suppressed GHn (10/14) in the 2011-12 cohort was higher compared to the 2006-09 cohort (3/13) (p = 0.02). Of the 46 patients with normal or low IGF-1 levels monitored over time, there was a 17.9% increase (p = 0.004) in IGF-1 concentration between 2008-9 and 2011-2012.

Conclusion: We found a significantly higher number of discordant IGF-1 and GHn results in the last 2 years as well as an 18% increase in IGF-1 levels from non-acromegalic patients monitored over time. This is consistent with the Immulite IGF-1 assay set-point which shifted upwards in 2010. Lot-to-lot reagent variability is a problem in immunoassays and clinicians need to be wary of this analytical issue particularly when other biochemical and clinical parameters are discordant.

**91  MS KYLIE CARVILLE**

**DELIVERY AND MONITORING OF HEPATITIS B BIRTH DOSE: BARRIERS AND STRATEGIES**
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Introduction: Perinatal transmission of hepatitis B virus leads to a sizeable proportion of chronic hepatitis B infections. Delivery of a hepatitis B vaccine ‘birth dose’ as soon as possible after birth (ideally within 24 hours) is the most efficient way to prevent perinatal transmission. In 2009 the World Health Organization (WHO) stated that all infants should receive this birth dose of hepatitis B vaccine. However it was acknowledged that weak immunization programs and primary health care systems in many countries create challenges to birth dose delivery and achievement of hepatitis B control goals.

Methods: We developed a background paper for a WHO technical meeting examining approaches to deliver the vaccine to more children on time. We reviewed approaches to delivery of the hepatitis B birth dose documented in both the peer reviewed and grey literature, with a focus on low and middle income countries.

Results: Barriers identified included lack of access to vaccine, to a vaccinator, missed opportunities for timely delivery, misconceptions about contraindications, fear of adverse events, opposition to delivery of vaccine by non-clinical or non-immunisation program staff, regulatory and political issues regarding out of the cold chain (controlled temperature chain) vaccine, acceptance of alternative injection devices, insufficient demand, difficulties identifying births and integrating systems not previously involved in giving vaccines, and poor recording of vaccine delivery. A number of countries have developed innovative strategies to address these barriers. Among the best documented are Indonesian projects incorporating delivery of birth dose at home and Chinese programs to improve hospital births and thus birth dose delivery.

Conclusion: Innovative strategies for the delivery of the birth dose need to be evaluated and shared. Documentation should include standard operating procedures for relevant staff.

92 DR BENJAMIN COWIE

HARNESSING HEALTH REFORM: NATIONAL ESTIMATES OF CHRONIC HEPATITIS B PREVALENCE, TREATMENT UPTAKE, AND OUTCOMES BY MEDICARE LOCAL

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Background: Medicare Locals are a key element of the Australian Government’s Health Reform Agenda, aiming to address local health priorities. The burden of chronic hepatitis B (CHB) in Australia – an estimated 218,000 people in 2011 – displays great geographic variability, and requires local programs targeting priority affected communities to address the steadily rising incidence of attributable cancer and mortality.

Methods: The prevalence of CHB by area was derived using risk group estimates applied to Census 2011 population data. HBV antiviral treatment by area was obtained from Medicare S100 data. Where available, these estimates were augmented with surveillance notifications and liver cancer incidence.

Results: Over a third of Australia’s 61 Medicare Locals have been profiled, comprising around 7.8 million people. Areas with the highest CHB prevalence include South Eastern Melbourne (7,122 people, 1.54%), Macedon Ranges-North West Melbourne (8,310 people, 1.38%), South West Sydney (13,160 people, 1.11%), and Greater Metro South Brisbane (9,466 people, 1.05%), which also demonstrate the highest liver cancer incidence. Overall treatment uptake is less than 3%, and even in areas with the highest levels (such as South West Sydney, 7.2%) only half of those estimated to currently require antiviral therapy are receiving it.

Conclusion: This ongoing project allows the development of targeted programs to address the needs of people living with CHB in the highest prevalence areas of the country. It also permits monitoring of treatment uptake over time in response to public health and clinical interventions, allowing evaluation of the impact of these at the local level.

93 DR BENJAMIN COWIE

HDV TESTING IN VICTORIA, AUSTRALIA 2000-2009: INSIGHTS INTO EPIDEMIOLOGY AND CLINICAL MANAGEMENT

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Background: Hepatitis D virus (HDV) only infects concurrently with hepatitis B virus (HBV), and is known to alter disease course, treatment options and likelihood of adverse outcomes in people living with chronic HBV. The epidemiology and clinical practices surrounding HDV in Australia are poorly understood, with no robust estimates of burden of disease or the extent of opportunistic testing.
Methods: Laboratory records of all HDV serological and RT-PCR testing in the state of Victoria were obtained for the period 2000-2009. Estimates of the number of cases per year were derived and compared with health department surveillance data, and records were analysed to evaluate testing patterns and follow-up for individual patients.

Results: 2,595 HDV serological tests were conducted on 2,318 individual patients residing in Victoria between 2000-2009; of these, 110 patients (4.7%) tested positive for HDV antibody or antigen, with both the number of patients positive and the number of tests steadily increasing between 2005 and 2009.

Of those patients who tested antibody positive, less than half (44 patients, 40%) were subsequently evaluated by qualitative HDV PCR, and the majority of those who were (29 patients, 70.5%) tested HDV RNA positive. Surveillance data show reasonable concordance with laboratory diagnoses, with 87 notifications for HDV made to the Victorian Department of Health in this period (79% of positive test results).

Conclusion: As an estimate of burden of disease, the proportion of positive tests observed (4.7%) corresponds strongly with current estimates of 5% HDV prevalence in those with HBV. Increased testing for HDV in Victoria over the last decade has resulted in an escalating number of HDV diagnoses and highlights the potential for undiagnosed HDV infection in those living with chronic hepatitis B, however gaps also remain in the appropriate testing and follow-up of patients known to be infected.

**94 DR MICHAEL MONTALTO**

SKIN SURFACE TEMPERATURE: AN OBJECTIVE MEASURE OF SEVERITY AND TREATMENT RESPONSE IN ACUTE SKIN AND SOFT TISSUE INFECTION

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Aim: There are few simple, objective ways to measure the severity and progress of skin and soft tissue infection (SSTI). We investigate the use of skin surface temperature in measuring the severity and the response to treatment of SSTI. This has not been reported previously.

Methods: An observational clinical study of patients admitted with SSTI for intravenous therapy. Medical staff were blinded to the main intervention. Skin surface temperature was measured daily at the point of maximum heat on the SSTI affected limb and at the corresponding point on the non-affected limb. This was done using a non-contact laser thermometer. We also collected the following patient data: core temperature, pulse, and blood pressure. We collected baseline data including: age; sex; presence of diabetes; presence of immunosuppressant drugs; presence of trauma or ulcers; microbiological swab results; blood culture results; and details of previous treatment.

The main outcomes were:
1. Temperature difference between SSTI affected and non-affected skin between day 1 and last day
2. Temperature difference between alternate limb girdle and SSTI affected limbs between day 1 and last day

Findings: 63 patients were included in the study. The mean age was 49.5 years (19-91) and 42 (66.7%) were men. The lower limb was affected in 47 patients (74.6%). 34 patients (54.0%) had taken oral antibiotics prior to presentation. The difference between affected and unaffected limb was 3.4 degrees C (95% CI 3.0-3.9) at day 1 and 2.1 degrees C (95% CI 1.7-2.6) on the last day, a difference of 1.3 degrees C (95% CI 0.7-1.9).

Between day 1 and the last day, there was a significant reduction in affected limb temperature (mean reduction of 2.4 degrees, 95% CI 1.9-3.0 p<0.001) and small drop in unaffected limb temperature (mean reduction of 0.9 degrees, 95% CI 0.3-1.5).

There was no change in patients’ BP (p=0.090 for systolic and p=0.777 for diastolic) and core temperature (p=0.067), but there was a significant drop in patients’ pulse (mean change 6 bpm, 95% CI 3.0-9.0, p<0.001).

Mean length of stay was 4.95 days.
Interpretation: Skin surface temperature may hold a useful role as a primary endpoint for the treatment of SSTI for clinicians and for researchers.

**95 MR TIM SHAW**

LIVING FAST AND DYING YOUNG: HEPATITIS C VIRUS DYNAMICS FROM A NEW PERSPECTIVE

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Nearly 3% of the global population is believed to be infected with the hepatitis C virus (HCV), a positive-stranded RNA virus that establishes potentially fatal persistent infection in a majority of cases. The recommended treatment for hepatitis C (pegylated interferon and ribavirin in combination) shows limited efficacy and frequently produces adverse
side effects. New anti-HCV drugs that have recently become available have greatly improved prospects for cure. Monitoring responses and surveillance for possible resistance to these drugs is vitally important. Regular monitoring of viral load is now an integral part of clinical management of hepatitis C. Mathematical models to describe and predict treatment responses have been devised, based on analyses of time-dependent, treatment-induced viral clearance. These invariably treat clearance as an essentially biphasic or multiphasic process, comprising an initial rapid exponential phase followed by one or more slower phases, attributed respectively to elimination of free virus and immune mediated-destruction and senescence of infected cells. Improved viral load assays, introduced in parallel with new drugs, have revealed seemingly more complex kinetics and inspired the development of increasingly sophisticated mathematical models. Specialist computing skills and software are required to implement and interpret analyses using current models, which limits their usefulness and makes more robust and facile alternatives highly desirable. We describe a new, conceptually and mathematically simple procedure for standardising, quantifying and comparing the clinical efficacy of antiviral drugs based on biochemical and genetic re-interpretation of the kinetics of viral clearance. We show that the quasispecies character of viral populations and the autocatalytic nature of viral replication justifies treatment of viral clearance as a continuous monotonic process which approaches an asymptotic, metastable equilibrium as the variants comprising the quasispecies are progressively eliminated at rates proportional to their replication rates. This approach, which we have used to analyse data generated during clinical trials of new, direct-acting anti-HCV drugs, makes it possible to quantify antiviral efficacy by means of simple three- or four-parameter rational equations. This facilitates comparisons between different treatment strategies and individual and population responses to specific treatments. Besides having powerful diagnostic and predictive potential, it provides a fresh perspective on the dynamics of inhibition of viral replication and antiviral drug action and can easily be implemented using a basic spreadsheet program such as Microsoft Excel.

96 MR BANG TRAN

THE HEPATITIS B SURFACE PROTEINS MAY PROMOTE THE DEVELOPMENT OF LIVER CANCER VIA UPREGULATION OF WNT/β-CATENIN SIGNALLING.

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Introduction: Chronic infection with hepatitis B or hepatitis C viruses is the major risk factor for development of liver cancer. Approximately 40% of liver cancer cases can be attributed to hepatitis B virus (HBV) infection, and the prevalence of HBV-associated HCC is rising at an alarming rate. The Wnt/β-catenin pathway has been causatively linked to various cancers, including liver cancer, with up to 60% of liver cancers showing active Wnt/β-catenin signalling. Despite the importance of this pathway in liver cancer, there are few studies examining the effect of HBV on Wnt/β-catenin signalling. The Aims of this study are to (1) characterise the Wnt/β-catenin signalling pathway in two HBV-permissive human liver cell lines (Huh7 and HepG2), to determine their suitability for HBV- Wnt/β-catenin signalling studies, and (2) use these cells to examine the potential impact of the HBV surface proteins on the Wnt/β-catenin signalling pathway in liver cancer.

Methods: To measure Wnt signalling, a TCF/β-catenin transcriptional reporter (sTOPflash) was co-transfected into cells with or without a plasmid encoding constitutively active β-catenin. Cells were then stimulated with Wnt3a in the supernatant, and luciferase activity (relative to renilla transfection control) was measured using the Promega Dual Luciferase assay.

Results: (1) We have confirmed that Huh7 cells have an intact, tightly regulated Wnt-signalling pathway in three ways; by demonstrating activation of TCF/β-catenin transcriptional activity following stimulation of pathway components at the cell surface, cytosol and nucleus. In contrast, HepG2 cells have high levels of constitutive activation due to mutated β-catenin. Despite constitutive activation, Wnt signalling in HepG2 cells can be further stimulated. (2) Using Huh7 cells, we have shown that co-expression of the HBV S protein greatly enhances receptor/ligand-mediated Wnt signalling. It also further increases the activity of co-transfected constitutively active β-catenin. This enhancement of Wnt signalling by HBV occurs in a dose-dependent manner.

Discussion and Conclusions: These results suggest that the HBV S protein stimulates additive Wnt/β-catenin signalling from both the receptor and transcription complex. This may be a mechanism by which HBV promotes the development of liver cancer. We are in the process of further characterising this interaction.

97 MR DUSTIN FLANAGAN

LGR5 AND FZD7 FUNCTION IN INTESTINAL EPITHELium REGENERATION
The adult mammalian intestinal epithelium undergoes constant self-renewal due to the unrelenting exposure to harsh chemical and mechanical stresses, and as a consequence is turned over every 3-5 days. This constant turnover of cells is maintained by stem cells that reside at the base of intestinal glands (called crypts) and are tightly regulated by the canonical Wnt signalling pathway. Intestinal stem cells are characterised by the expression of G-protein coupled receptor Lgr5. It was demonstrated that Lgr5+ stem cells are capable of self-renewal and generating all cell lineages of the intestinal epithelium.

The intestinal epithelium has a remarkable capacity to regenerate following DNA damage, acute inflammation, surgical resection and genetic ablation of genes required for intestinal homeostasis. Intestinal regeneration is characterised by a marked increase in proliferation within the crypt, leading to transient crypt enlargement. In wild type mice, exposure to 14 Gy whole body irradiation results in ablation of the epithelium by 48 hours. At 72hrs post irradiation the epithelium begins to regenerate, and large highly proliferative crypts develop. In mice that are heterozygous for Lgr5, the regeneration process is disrupted/retarded as Lgr5+/− mice display a lack of proliferative regenerating crypts 72hr post irradiation. Similar attenuated regeneration is observed in Fzd7 knock-out mice. Furthermore, we observe a decrease in canonical Wnt signalling in parallel with an increase in cell cycle arrest in irradiated Fzd7 knock-out mice. Following from the recent discovery that Lgr4 and Lgr5 function as R-spondin receptors to potentiate Wnt/Fzd signalling, we demonstrate a functional defect in intestinal regeneration when Fzd7 is deleted or Lgr5 is reduced, confirming this process requires competent Wnt/Fzd signalling.

INVESTIGATION OF A NEW MECHANISM OF PATHOGENESIS IN COLORECTAL POLYPOSIS

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Purpose: Germline mutations in the APC gene underlie FAP. APC is best characterised for its role as a negative regulator of Wnt-signalling, where APC forms a “destruction” complex with the scaffolding protein AXIN1, facilitating degradation of β-catenin. Abrogated Wnt-signalling is recognized to be important in both gut homeostasis and in driving colorectal tumourigenesis. Clinically, there are a significant number of polyposis patients in which pathogenic APC or MUTYH mutations have not been identified. The polyposis phenotype raises the possibility that other genes may be mutated. We propose that AXIN1 mutations will result in compromised Wnt-signalling mediated via interactions with the β-catenin destruction complex.

Methods: We screened the AXIN1 gene for germline mutations in a cohort of 256 patients with a polyposis phenotype, but lacking pathogenic APC and MUTYH mutations using Sanger sequencing and deletion screening analyses.

Results: 6 missense mutations were identified in 15 patients, and 12 rare synonymous or intronic changes were identified in 21 patients and flagged as possible splice site mutations by multiple in silico analyses. Conservation and in silico analyses of missense mutations provided preliminary evidence that these mutations may affect AXIN1 function. Furthermore, each of the missense mutations were located in critical binding domains of AXIN1 indicating a functional consequence. In vitro protein functional studies were done in patient derived cell lines and colonic epithelial cells to determine pathogenicity of the AXIN1 missense mutations with respect to interference with Wnt-signalling, equivalent to mutations in the APC gene. These in vitro studies suggested that one of the AXIN1 missense mutations attenuate AXIN1 function, and hence may deregulate the Wnt-signalling pathway, leading to the observed polyposis phenotype.

Conclusion: Sequence changes in interacting domains of the Wnt-signalling pathway scaffolding gene AXIN1, coupled with preliminary functional studies, suggest AXIN1 may be implicated in patients with multiple adenomas. Further clinical and functional studies are needed to consolidate these findings. Identification of a third gene in polyposis would have immediate clinical impact and be of substantial importance in CRC management, for both familial and non-familial CRC.

VANCOMYCIN DOSING IN HAEMODIALYSIS PATIENTS: IS A LOADING DOSE REQUIRED?

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Aim: To examine both the starting doses of vancomycin used in haemodialysis patients and subsequent initial vancomycin levels attained to determine if a loading dose of vancomycin is warranted in this patient population.
Method: A retrospective audit of vancomycin use in patients receiving haemodialysis over a 6 month period (January to June 2010) was conducted. Haemodialysis patients who were initiated on vancomycin and had at least one vancomycin level taken during the study period were included. Patients who received a stat dose of vancomycin were excluded from this analysis.

Results: All patients had high flux haemodialysis and used the Gambro Polyflux H dialyzer. Further doses of vancomycin were administered if the daily spot level was < 20mg/L.

A total of 23 patients were included. 18 patients were receiving vancomycin for either proven or suspected bacteraemia with the remaining patients receiving vancomycin for arteriovenous fistula or graft infections (2), diabetic foot infections (2) or MRSA pneumonia (1).

22 patients (96%) received an initial vancomycin dose of 1g, the remaining patient received 1.5g. 15 patients (65%) had a vancomycin level < 15mg/L before the second dose. 11 of the 15 initial spot levels were taken the day after the first dose.

14 patients (61%) received vancomycin the day after their initial dose, with only two patients not receiving vancomycin because their spot level was > 20 the following day (neither exceeded 25mg/L).

In a subset of 4 patients receiving vancomycin during haemodialysis only, 2 patients had levels ≤ 10mg/L prior to receiving their second dose at the next dialysis session.

Conclusion: This study suggests that a vancomycin loading dose greater than 1g is warranted in haemodialysis patients on high flux dialysis. A spot level should be checked no later than 24 hours after the initial dose of vancomycin in haemodialysis patients.

100 A/PROF TIM HEWITSON

ESTROGENS DO NOT PROTECT FROM AGEING NOR INJURY-RELATED KIDNEY FIBROSIS

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Background: Although previous studies have suggested that estrogens protect against organ fibrosis, most have used pharmacological doses, and have not accounted for indirect activation of estrogen receptors through aromatase-mediated conversion of testosterone to 17beta-estradiol (the most potent form of estrogens). We recently demonstrated that 12-14-month old male ArKO mice, which lack estrogens but have 5-10 times the testosterone levels of normal (ArWT) male mice, had a significant increase in renal fibrosis. However, we do not know if this is a protective effect of estrogens or a detrimental effect of testosterone.

Aim: To determine the role of estrogens in renal fibrosis, we examined the pathology of ageing and injured female aromatase gene-knockout (ArKO) mice, which lack circulating and stored estrogens, while having normal female levels of testosterone.

Methods: Female ArKO and ArWT mice were either aged to 15-months or subjected to unilateral ureteric obstruction (UOO) at 6-8 weeks of age. Tissue was collected from ageing mice at 6- and 12-15-months; or injured mice at day (D) 0, 3 and 9 post-UOO; and assessed biochemically and histologically for changes in kidney size and fibrosis.

Results: At 12-15 months, ArKO mice had small kidneys (p<0.05), but equivalent collagen concentration (% dry weight) and histology to ArWT mice. UUO increased collagen concentration by 36+/−6% (mean+/−SE) at D3 (p<0.05 vs D0) and 80+/−12% at D9 (p<0.01 vs D0, p<0.05 vs D3), with no difference between genotypes.

Conclusions: Physiological concentrations of estrogens do not protect the ageing nor injured kidney from fibrosis progression, suggesting that testosterone rather than estrogens regulate senescence- and disease-related renal scarring.

101 PROF STEPHEN HOLT

FETUIN-CONTAINING CALCIPROTEIN PARTICLES ARE FORMED IN SITU IN PERITONEAL DIALYSIS FLUID AND MAY CONTRIBUTE TO PERITONEAL INFLAMMATION IN PERITONEAL DIALYSIS PATIENTS.

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Background: Peritoneal Dialysis (PD) accounts for ~20% of all dialysis in Australia/New-Zealand. The technique itself damages the peritoneal membrane over time and results in inflammation with an influx in fibroblasts, loss of mesothelial cells, fibrosis and sometimes calcification. These changes eventually result in a loss of membrane function, resulting in technique failure.
Fetuin-A (Fet-A) is synthesised in the liver and circulates at high concentrations. Fet-A knockout animals develop ectopic mineral deposition and poor bone development. In humans, Fet-A deficiency has been consistently associated with increased arterial calcification and higher mortality rates. In the circulation, Fet-A forms high molecular weight complexes called calciprotein particles (CPP), which contain calcium phosphate nanocrystals. Initially, these form as small spherical complexes which over time become elongated and more needle shaped, between 100-200nm in length. These CPP may be cleared by macrophages after uptake by the scavenger receptor-A. CPP are detectable in the serum of patients with chronic kidney disease and/or inflammation, but not normal controls and in vitro application of CPP to macrophages causes inflammatory cytokine and oxidant species generation. CPP have additionally been reported in the PD fluid of patients with calcific peritonitis. Since these particles are too big to pass even through large peritoneal membrane pores (~25nm), we tested the hypothesis that CPP might be formed in situ in peritoneal fluid.

Methods: In a pilot study we measured CPP in spent dialysate fluid (PDF) and in the serum of 20 patients undergoing PD without obvious complication. Results are expressed as mean(SD).

Results: Higher concentrations of Fet-A were found within PDF than might be expected by simple diffusion from the circulation (68(48) vs 45(13) mg/L (p<0.05). Measuring Fet-A/albumin in serum and PDF respectively was 5(1) vs 81(44) mg/g (p<0.0001). The CPP present in PDF are nascent (spherical) CPP and not of the same morphology (spindle shaped) found in the circulation.

Conclusion: Fetuin-A is produced or sequestered locally within the peritoneum, where it contributes to CPP formation within the peritoneal cavity. CPP may interact with macrophages to contribute to peritoneal inflammation.

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**FETUIN-A-CONTAINING CALCIPROTEIN PARTICLES REDUCE MINERAL STRESS IN THE MACROPHAGE**

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Background: The formation of fetuin-A-containing calciprotein particles (CPP) may facilitate the clearance of calcium phosphate nanocrystals from the extracellular fluid. These crystals may otherwise seed extra-osseous mineralization. Fetuin-A is a partially phosphorylated glycoprotein that plays a critical role in stabilizing these particles, inhibiting crystal growth and aggregation. CPP removal is thought to be predominantly mediated by cells of the reticuloendothelial system via type I and type II class A scavenger receptor (SR-A/I/II). Naked calcium phosphate crystals are known to stimulate macrophages and other cell types in vitro, but little is known of the effect of CPP on these cells.

Methods and Results: We report here that CPP induce expression and secretion of tumour necrosis factor (TNF)-α, interleukin (IL)-1β in murine RAW 266.7 macrophages. Importantly, however, CPP induced significantly lower cytokine secretion than hydroxyapatite (HAP) crystals of equivalent size and calcium content. Furthermore, CPP only had a modest effect on macrophage viability and apoptosis, even at very high levels, compared to HAP crystals, which were strongly pro-apoptotic at much lower levels. Fetuin-A phosphorylation was found to modulate the effect of CPP on cytokine secretion and apoptosis, but not uptake via SR-A/I/II. Prolonged exposure of macrophages to CPP was found to result in up-regulated expression of SR-A/I/II.

Conclusions: CPP formation may help protect against some of the pro-inflammatory and harmful effects of calcium phosphate nanocrystals, which may represent a natural defense system for calcium mineral stress. However, in pathological states where production exceeds clearance capacity, these particles may still stimulate pro-inflammatory and pro-apoptotic cascades in macrophages, which may be important in the pathogenesis of vascular calcification.

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**FETUIN-CONTAINING CALCIPROTEIN PARTICLE LEVELS CAN BE REDUCED BY DIALYSIS, SODIUM THIOSULPHATE AND PLASMA EXCHANGE. POTENTIAL THERAPEUTIC IMPLICATIONS FOR CALCIPHYLAXIS?**

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Background: Fetuin-A is an important regulator of physiological and pathological mineralisation. High concentrations of fetuin-A (Fet-A) are found in bone, and circulating Fet-A has been shown to protect from ectopic mineralisation. In patients with chronic inflammation and with chronic renal impairment, Fet-A is detectable within large macromolecular complexes called calciprotein particles (CPP). CPP are large (50-200nm) nanocrystals of calcium.
phosphate surrounded by a predominantly Fet-A protein ‘shell’. CPP formation may protect cells against the pro-inflammatory and pro-apoptotic effects of naked crystalline calcium phosphate. We have previously demonstrated that in calciphylaxis, a condition associated with severe vascular calcification and a very poor prognosis, a very high proportion of serum fetuin-A circulates as CPP (CPP%). Serum CPP% might therefore be used as a diagnostic marker and/or as a biomarker for the ongoing underlying pro-calcific process seen in this disease. Furthermore, treatment of the condition is hindered by the lack of a reliable target to monitor. Treatments advocated to date include increased duration/frequency of haemodialysis (HDx), sodium thiosulphate (STS) infusion and plasma exchange (PEx). We were therefore interested in whether other therapies that have been previously reported to be useful for this condition would change serum CPP%.

Methods: We measured serum CPP% after HDx, PEx, and after STS infusion.

Results: We showed that HDx reduces serum CPP% but not sustainably so. The addition of STS infusion during HDx further reduced CPP%, but infusion between HDX sessions had no significant sustained reduction. PEx provided additional benefit, reducing CPP% between HDX sessions.

Conclusion: We have identified a biochemical marker that might help monitor treatments or design therapies for this condition. Whether CPP are involved directly in the pathogenesis of vascular calcification or calciphylaxis remains to be elucidated.

THE FATE OF MESANGIAL IGA IN THE DONOR KIDNEY: EXPERIENCE AT THE ROYAL MELBOURNE HOSPITAL.

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BACKGROUND: Some authors claim that the presence of mesangial IgA (mIgA) in the donor kidney is associated with an increased risk of recurrent IgA glomerulonephritis in transplant recipients, particularly if the primary disease of the recipient was IgAGN (plgAGN). AIM: To identify patients who had mIgA present in their donor kidney in the immediate post reperfusion biopsy (time zero biopsy) and to determine a) its fate and b) its impact on transplant and recipient survival. METHODS: Logbooks from 2000 to 2005 were retrospectively consulted to identify patients whose post reperfusion biopsies were positive for mIgA. Database searches were then conducted with particular emphasis on subsequent renal biopsies, serum eGFR and haematuria. Follow-up was until 2012. RESULTS: Twenty-one patients had mIgA in their post reperfusion biopsy. In subsequent biopsies 4 days to 3 years post transplant, 18 patients had no mIgA. Two patients who did not have follow-up biopsies had normal eGFR, no haematuria and appear to be disease-free. One patient had graft failure secondary to obstruction after four years of disease-free survival without evidence of recurrent IgA in the transplant nephrectomy. Seven of the patients with mIgA in their post reperfusion biopsy had plgA GN. Two of these did develop recurrent IgA glomerulonephritis, however this occurred some time after the mIgA initially present in the donor kidney had disappeared. Of the patients who did not have plgA GN as the cause of their ESRF, none developed IgA GN. Patients were disease-free and dialysis-free for a median of 7 years. CONCLUSIONS: We conclude that the presence of mIgA in the donor kidney does not negatively impact on graft or recipient survival. We have shown that mIgA in the donor kidney disappears within a variable time frame. No adverse events can be directly attributable to the presence of mIgA in the donor kidney. Patients were disease-free and dialysis-free for a median of 7 years. The study supports the theory that factors inherent in the renal parenchyma are not involved in the pathogenesis of IgA GN. We confirm that the major risk factor for developing IgA glomerulonephritis in renal allografts is plgA GN.

SEASONAL CHANGES IN THE PATHOLOGY MARKERS OF HAEMODIALYSIS PATIENTS: IS POTASSIUM AN EXAMPLE?

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Background: Seasonal changes in the blood pressure, biochemistry and haematology of haemodialysis and peritoneal dialysis patients have been described. The aetiology of these variations, which impact on clinical evaluation, treatment and outcomes, are poorly understood. This study explores seasonal potassium changes in a cohort of haemodialysis patients looking at potential differences in diet as a contributing factor.

Hypothesis: We explored the hypothesis that during the months of the year when potassium rich foods are plentiful, Mediterranean born patients would demonstrate higher serum potassium levels than their Australian born counterparts.

Methods: To determine the accuracy and extent of this assumption, we examined the average monthly serum potassium levels in our Greek (n=20) and Italian (n=24) born haemodialysis patients aged >65 years, over 18 months (Jan 2010- June 2011). These were compared to a similar group of Australian born dialysis patients (n=86). All patients
had pre-dialysis biochemistry at least monthly. For each patient, the average monthly level was calculated from all measurements taken (mean±SE mmol/l).

Results: Serum potassium levels in Australian born patients ranged from 4.56±0.09 (Feb 2010) to 4.99±0.07 (Feb 2011). The fluctuation in Mediterranean born patients was greater with serum potassium peaking in March 2010 (5.12±0.10) and Feb 2011 (5.46±0.14) compared to a low of 4.55±0.09 mmol/l in Oct 2010. During February 2011, 10% of Mediterranean patients, and 5% of Australian born patients, had serum potassium levels > 6 mmol/l.

Conclusion: Our longitudinal analysis confirms that serum potassium levels show seasonal variation. There are variations in these fluctuations which may reflect dietary differences based on food tradition. In the case of our Greek and Italian patients, this may be significant and can reach very high levels. Further studies may elucidate potential and modifiable causative factors.

106  PROF JUDY SAVIGE

COLLAGEN III INTERACTOME REVEALS COMMON MECHANISMS FOR HETEROTYPIC FIBRIL ASSEMBLY AND A SHARED FUNCTIONAL DOMAIN ORGANIZATION WITH COLLAGEN I BUT GREATER POTENTIAL FOR HEMOSTASIS REGULATION

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Background: Collagen III is critical in maintaining the integrity of blood vessels and distensible organs, and in hemostasis. Collagen I forms heterofibrils with collagen III and progressively replaces collagen III in embryonic development and wound healing.

Aims: This study compared collagen III and collagen I linear protein maps (‘interactomes’) including charge distribution, structural features, ligand-binding sites, and missense mutations. Results: The collagen III D-period has a nearly identical charge distribution and an identical structural arrangement to collagen I. The major ligand binding regions, cell interaction domain, and fibrillogenesis and enzyme cleavage domains are at the same locations. However collagen III is distinguished by two hemostasis domains, with binding motifs for von Willebrand factor, or for integrin, the platelet binding octapeptide and glycoprotein VI. The distribution of missense mutations causing Ehlers-Danlos syndrome IV is also non-random reminiscent of collagen I and osteogenesis imperfecta. Mutations in at least five other genes causing Ehlers-Danlos syndrome code for further collagen III binding partners.

Conclusions: The close resemblance of collagen III and collagen I architecture allows heterotypic fibril formation, and substitution of one molecule for the other. Collagen III’s multiple binding sites for hemostatic ligands accounts for the bleeding tendency in Ehlers-Danlos syndrome.

107  PROF JUDY SAVIGE

MICROVASCULAR DISEASE IS INCREASED IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA (OSA)

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Background and Aims: Microvascular abnormalities in the retina reflect systemic small vessel disease. This study used retinal examination to compare the prevalence of microvascular disease (severity of changes and calibre) in patients with obstructive sleep apnoea (OSA) or Chronic obstructive pulmonary disease (COPD).

Patients and Methods: Patients were recruited from the Respiratory clinic and wards of a metropolitan teaching hospital. OSA was diagnosed on a sleep study (apnoea: hypopnoea index >5) in an accredited diagnostic laboratory. COPD was diagnosed with a forced expiratory ratio (FER) <70%. Patients were assisted to complete a questionnaire of their medical details and medications, including their use of continuous positive airway pressure (CPAP).

All participants underwent retinal photography using a non-mydriatic camera (KOWA, KOWA Japan). Images were graded for microvascular retinopathy (Wong and Mitchell classification) by an ophthalmologist and a trained observer. Images were sent to the Centre for Eye Research Australia for measurement of the retinal arteriole and venular calibre by a grader using Knudtson’s revised version of the Parr-Hubbard formula.

Statistical analysis was performed using Stata version 11.2 software (Stata Corp), and multivariate analysis with backwards logistics regression.

Results: Seventy-nine patients with OSA and 132 with COPD were recruited. Patients with OSA alone were younger (mean difference 7.4 years, 95%CI 4.17 to 10.06, P <0.01), had a higher BMI (mean difference 8.80 kg/m2, 95%CI -
10.76 to -6.58, P <0.01) and were less likely to be smokers (OR 0.06, 95%CI 0.02 to 0.15, P <0.01) than those with COPD. They did not have hypertension or diabetes more often. Patients with OSA had more microvascular disease than those with COPD (OR 9.90, 95%CI 2.29 to 42.90, P <0.01). In addition, their arterioles (mean difference 18.00μm, 95%CI 12.88 to 23.08, P <0.01) and venules (mean difference 25.30μm, 95%CI 17.09 to 33.52, P <0.01) were narrower. These changes were not worse with more severe OSA and were not reversed with the use of CPAP. Microvascular retinopathy was still more common and the arteriolar and venular narrowing persisted in patients with OSA after adjusting for age, BMI, hypertension, smoking and dyslipidemia.

Discussion and Conclusions: Patients with OSA have increased small vessel disease compared with patients with COPD, with worse microvascular retinopathy and narrower vessels. Unexpectedly this narrowing was not related to OSA severity nor was it reversed with CPAP treatment.

HOW NONSENSE MUTATIONS IN THE COL4A5 GENE CAUSE X-LINKED ALPORT SYNDROME

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Background: Alport syndrome is an inherited progressive renal failure associated with hearing loss, lens cataracts and retinopathy, that affects one in 10,000 individuals. X-linked disease accounts for 85% of patients and is due to COL4A5 mutations. Fifty% of all mutations are nonsense variants, and are associated with a more severe phenotype. In other inherited collagen diseases, nonsense mutations have their effect through ‘nonsense-mediated decay’. The aim of this study was to determine whether nonsense mutations in X-linked also resulted in nonsense-mediated decay.

Methods: Levels of collagen IV a1 – a6 chain mRNA were quantitated in the urine of 2 patients with X-linked Alport syndrome due to nonsense mutations. Cells were then established from skin biopsies from males and females with X-linked Alport syndrome. Control cell lines were also established from normal non-haematuric individuals.

The growth curves of these cell lines were examined and levels of collagen IV a3, a4 and a5 mRNA quantitated using real time (RT-)PCR (7500 Real Time PCR System, Applied Biosystems). Results in each RT-PCR assay result were compared with GAPDH, and performed in duplicate on 3 occasions. Levels of mRNA corresponding to the pro- and antiapoptotic pathways (caspase 3, BAD and Bcl2) were also quantitated.

Collagen IV mRNA levels were also measured both before and after incubation with protein synthesis inhibitors (0.1 mg/ml cycloheximide, 0.1 mg/ml anisomycin, or 0.1 mg/ml puromycin).

Results: Levels of the a5 collagen IV chain mRNA were reduced in the urine of males with X-linked Alport syndrome and nonsense mutations. In cell lines from affected males and females with X-linked disease, levels of a5 collagen IV mRNA were lower than in normals. Levels of a3 and a4(IV) collagen mRNA were also reduced.

Levels of a5(IV) mRNA were increased in cell lines from males with X-linked Alport syndrome after treatment with protein synthesis inhibitors. There was no increase in the pro- or antiapoptotic pathways in the untreated Alport cell lines nor after incubation with protein synthesis inhibitors.

Conclusions: The low levels of collagen IV a5 mRNA and the increase after incubation with protein synthesis inhibitors confirmed a role for nonsense-mediated decay. The use of therapeutic agents that inhibit nonsense-mediated decay may mitigate disease severity in patients with Alport syndrome without an increase in adverse events mediated by apoptosis.

This work was supported by a grant from the Alport Syndrome Foundation of Australia.

WHAT IS HAEMODYNAMIC STABILITY? THE IMPORTANCE OF ‘TIME’ IN ‘CHANGE OVER TIME’.

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Aims: Whilst fundamental to many branches of clinical medicine, the concept of haemodynamic stability is not readily defined by quantitative measures. During haemodialysis (HD) significant hypo or hypertension is arbitrarily defined by a symptomatic change in systolic pressure (SBP) >20mmHg and associated with significant mortality excess. Such definitions are heavily reliant upon patient self-report and ignore the importance of appropriate intraobservation time-periods to frame the diagnosis. We examined the frequency of intradialytic SBP variability to determine the effect of progressively lengthening reference time-frames on the diagnostic sensitivity.

Method: The comprehensive beat-to-beat SBP record of 38 HD sessions was recorded in nominally ‘stable’ asymptomatic HD outpatients (68% male, 18% diabetic). The continuous SBP time-series was analysed in the context of 3 time-windows, defined ‘short’, ‘medium’, and ‘long’ by the pulse-period lengths of 100, 500 and 1,000 heart-beats respectively. To define ‘significant’ BP variability the absolute cutoff of 20mmHg systolic was used. A rate-of-
change momentum oscillator algorithm compared the magnitude and direction of SBP change against a continuously moving baseline for each respective timeframe.

Results: A single session did not demonstrate any occurrence of variability exceeding threshold significance. All other HD treatments (97%) recorded one or more significant swings in pressure over one or more time-windows. The total number of captured events was 193, 369 and 316 for 100, 500 and 1,000 beat observation widths respectively. Peak sensitivity for capturing intradialytic SBP swings occurred in the medium term. The frequency of suprathreshold episodes was (mean±SEM) 5.08±1.08, 9.71±0.98, and 8.31±0.76 for the respective periods. Over the shortest timeframe, sudden rises were more common than sudden fall (57% Vs 43%) however this ratio reversed with lengthening of the framing period. Despite the frequency of significant SBP variability, only a single episode was associated with clinical symptoms. Applying a diagnostic threshold of +15% change in SBP (approximating a 20mmHg fall at 140mmHg) saw a reduction in the incidence of major swings due to higher levels of SBP (69% of dialyses had intradialytic mean pressures exceeding 140mmHg.) For those with lower baseline pressures the pickup rate was increased however the clinical implications remain unclear at an individual patient level.

Conclusion: Clinically silent SBP variability during ‘stable’ HD is exceedingly common and unrecognised in clinical practice when strict pressure criteria are applied. Appropriate timing between observations is paramount to framing the diagnosis. The relative importance of absolute versus relative (percentage based) pressure thresholds warrants further consideration.

110 DR SIMON LAU

CERVICAL SPINAL CORD INJURY AT THE VICTORIAN SPINAL CORD INJURY SERVICE: THE LAST DECADE

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Introduction: Cervical Spinal Cord Injury (CSCI) is a significant medical and socioeconomic problem. In Victoria, Australia, there has been limited research into the incidence of CSCI. The Austin Hospital and Victorian Spinal Cord Injury Service (VSCIS) is a tertiary referral hospital that accepts referrals for surgical management and ongoing neurological rehabilitation for south eastern Australia.

Methods: This was a retrospective review of medical records from January 2000 to January 2010 of all patients who underwent surgical management of acute CSCI in the VSCIS catchment region, with a total sample size of 206.

Outcome measures included: demographics, method of injury and associated factors (like alcohol) and neurological status.

Results: Men were much more likely to have CSCI than women with a 4:1 ratio, and the highest incidence of CSCI for men was in their 20s, who were at greater risk of complete injury. The most common cause of CSCI was transport related (51%), followed by falls (20%) and water-related incidents (16%). Falls were more prevalent among those >50 years. Alcohol was associated in 22% of all CSCIs, including 42% of water related injuries. Water related injuries only involved people <50 years.

Discussion: Our retrospective epidemiological study identified at-risk groups presenting to our spinal injury service. Young males in their 20s were associated with an increased risk of transport related accidents, water related incidents in the summer months and accidents associated with alcohol. Another high risk group were men >50 years who suffer falls from height. Public awareness campaigns should target these groups to lower incidence of CSCI.

111 DR DAVID CANTY

THE IMPACT OF PRE-OPERATIVE FOCUSED TRANSTHORACIC ECHOCARDIOGRAPHY IN EMERGENCY NON-CARDIAC SURGERY PATIENTS WITH KNOWN OR RISK OF CARDIAC DISEASE

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Background: Cardiac complications are the leading cause of postoperative mortality in non-cardiac surgery. Emergency surgery patients frequently have cardiac disease and an abnormal haemodynamic state but are there is often inadequate time for adequate evaluation and optimisation. Transthoracic echocardiography (TTE) provides valuable information but is frequently unavailable or causes inconvenient delays to surgery. Anaesthetists are developing skills in point-of-care focused TTE. The aims of this study were to determine feasibility of preoperative focused TTE and whether it results in important changes to diagnosis and management.

Methods: This prospective observational study investigated the effect of focused echocardiography in 99 patients who had suspected cardiac disease or were > 65 years old, and were scheduled for emergency non-cardiac surgery. The treating anaesthetist completed a diagnosis and management plan before and after echocardiography, which was
performed by an independent anaesthetist. Ethics approval was obtained from the institution and informed consent obtained from all patients.

Results: Clinical examination rated cardiac disease present in 75%; the remainder were asymptomatic. The cardiac diagnosis was changed in 67% and the management plan in 44% of patients after echocardiography. Cardiac disease was identified by echocardiography in 64% of patients, which led to a step-up of treatment in 36% (4% delay for cardiology referral, 2% altered surgery, 4% intensive care and 26% intra-operative haemodynamic management changes). Absence of cardiac disease in 36% resulted in a step-down of treatment in 8% (no referral 3%, intensive care 1% or haemodynamic treatment 4%). Haemodynamic management changes included the use of invasive monitoring, vasoressor infusions and intravascular fluid management. Echocardiography revealed important cardiac disease (and resulting step up in treatment) that was missed by clinical examination in 7% of patients.

Conclusion: Pre-operative focused TTE in patients admitted for emergency surgery and with known cardiac disease or suspected to be at risk of cardiac disease frequently alters diagnosis and management.

112 DR DAVID CANTY

THE IMPACT OF PREOPERATIVE FOCUSED TRANSTHORACIC ECHOCARDIOGRAPHY IN FRACTURED NECK OF FEMUR SURGERY: A RETROSPECTIVE COHORT STUDY

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Background: Hip fracture surgery has one of the highest mortality and morbidity of all operations. Heart disease is common in this elderly population, which is often unrecognised and inadequately treated. Anaesthetists often face a difficult decision whether to proceed with early surgery, associated with reduced mortality, or delay surgery for further cardiac evaluation. Preoperative focused transthoracic echocardiography (TTE) by anaesthetists is feasible, more accurate that physical examination and frequently influences diagnosis and management without delay (1) but reduced mortality has not been demonstrated.

Methods: Postoperative mortality of 64 hip fracture surgery patients at risk of cardiac disease who received preoperative TTE in two reported observational studies at Royal Melbourne (1) and Royal Hobart Hospitals (2) was retrospectively compared to 66 randomised historical controls with similar risk factors without preoperative TTE. Ethics approval was obtained as a quality assurance project not requiring written consent.

Results: Patients were well matched with measured risk factors. Mortality was reduced in the TTE group compared with controls over both the 30 day (4.7% v 15.2%, log rank p=0.047) and 12 month postoperative period (17.1% v 33.3%, log rank p=0.031). There was also a significant reduction in the hazard of death over the 12 month period after adjusting for known risk factors (hazard ratio 0.41, 95% CI 0.2,0.85, p=0.016). TTE was not associated with a delay in surgery (echo group 1.7 days, SD 1.9 days and control group 1.4 days SD 1.2 respectively, p=0.605). The cardiac diagnosis was changed in 78% and the management plan in 52% of patients after echocardiography. Cardiac disease or abnormal haemodynamic state was identified by TTE in 75% of patients including hypovolaemia (34%), cardiac failure (20%), aortic stenosis (14%) and pulmonary hypertension (11%). Management changes included decisions to proceed or delay surgery (5%), use of invasive monitoring (8%), fluid bolus or restriction (23%), altered anaesthetic technique (6%), vasoressor infusion (8%), and postoperative high dependency care (2%).

Conclusion: Preoperative focused TTE by anaesthetists may reduce mortality in patients at increased cardiac risk who require fractured neck of femur surgery. This hypothesis needs to be tested in an adequately powered randomised trial.

113 DR DAVID CANTY

THE IMPACT OF ROUTINE NORADRENALINE INFUSION ON HAEMODILUTION AND BLOOD TRANSFUSION IN CARDIAC SURGERY

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Background : Haemodilution(1) and blood transfusion(2) are common and are associated with poor outcome after cardiac surgery, and considerable efforts are made to avoid them(3). We hypothesised that routine intravenous noradrenaline infusion during anaesthesia and on-bypass cardiac surgery would reduce intraoperative haemodilution and requirement for red cell transfusion by prevention of venodilation, vasodilation and intravascular fluid therapy.

Methods: Two cohorts of consecutive cardiac surgery patients with a single surgeon were retrospectively reviewed for perioperative haemoglobin and creatinine concentrations and red cell transfusion. Patients in the noradrenaline group (n=72, in 2010) all received standardised haemodynamic management with noradrenaline infusion (3-5 mcg.min⁻¹, 0.04 – 0.07 mcg/kg/min) from anaesthetic induction, throughout surgery and continued into the postoperative period.
In the absence of blood loss, haemodynamic stability was achieved using vasopressors and inotropes rather than fluid administration. Controls (n=94, in 2005) received selective noradrenaline infusion post CPB for persistent hypotension and vasodilation. The target transfusion trigger was Hb < 70.0 g/L.

Results: Haemoglobin concentration (mean g/L±SD) was higher in the noradrenaline group compared with controls intraoperatively, p<0.0001, despite lower baseline values (139±19 vs 133±15, P=0.028) and was higher at time of ICU admission. Fewer units of red cells were transfused in the noradrenaline group intraoperatively (0.2±0.6 units/patient) compared with controls (0.5±1.47, p=0.041), a reduction of 62%. Maximum postoperative rise in serum creatinine concentration (micromol/L) was not significantly different (noradrenaline group 26±32, controls 30±57, p=0.49 and at discharge 3±53 vs. 5±30, p=0.39). Noradrenaline group patients received more extensive surgery (p=0.042) and no aprotinin compared to 74% of controls, and therefore may have been at increased risk of bleeding.

Conclusions: During on-bypass cardiac surgery, routine noradrenaline infusion was associated with reduced haemodilution and intraoperative red cell transfusion without increased postoperative serum creatinine compared to controls. This deserves definitive evaluation with an adequately powered randomised controlled trial.

114 DR NIKHIL SAPRE

A MICRORNA SIGNATURE IN URINE CAN IDENTIFY THE PRESENCE OF BLADDER CANCER IN PATIENTS UNDERGOING SURVEILLANCE

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Introduction and Objective: The long-term surveillance mandated for non-muscle invasive bladder (NMIBC) patients is expensive and resource intensive and no non-invasive biomarker currently exists to identify patients with disease recurrence. The objective of this study was to determine if microRNA (miR) profiling of urine can identify the presence of transitional cell carcinoma (TCC) in the bladder in patients undergoing surveillance and to compare its test performance characteristics to that of flexible cystoscopy.

Materials and Methods: We screened 60 patients, which included 30 non-recurers (patients with a history of TCC but no recurrence at cystoscopy) and 30 recurrers (patients with TCC identified at cystoscopy) using a panel of 16 microRNAs (miRs) that were over expressed in bladder cancer tissue in previous studies. Total RNA was extracted from urine using the mirVana kit (Ambion, Austin, TX, USA) and preselected Taqman miR assays used for profiling by real time quantitative polymerase chain reaction (RT-qPCR). All reactions were performed in triplicate and the median included in the final analysis. Data analysis was performed using PASW v18.0 and machine learning approaches to test the predictive ability of individual and a combination of miRs profiled in urine. Specifically for machine learning, a centroid classifier and centroid feature selection procedure was trained using a three-fold cross validation approach and performance was measured using the area under the receiver operator characteristic curve (AUC).

Results: Individually miR 34a (p<0.001, AUC=0.80), miR 205 (p=0.001, AUC=0.77), miR 16 (p=0.001, AUC=0.75), miR 200c (p<0.001, AUC=0.75), miR 106b (p=0.007, AUC=0.7), miR 221 (p=0.006, AUC=0.71) and miR 21 (p=0.001, AUC=0.70) were able to distinguish the recurrers from the non-recurrers. However, the best predictor of the presence of TCC was achieved using a combination four miRs (miR 34a, miR 205, miR 16, and miR 200c) measured in urine (AUC=0.81). This combination of four microRNAs in urine was a better predictor of presence of cancer in the bladder than any individual microRNA. The difference in miR expression profiles between the recurrers and non-recurrers was highest for patients with presence of high volume and high-grade disease.

Conclusion: This study suggests that urinary profiling of microRNAs may allow their use in the surveillance setting to detect presence of TCC in the bladder as an alternative to flexible cystoscopy. Validation of results in an independent cohort is currently underway.

115 DR KARY SUEN

ACUTE COLONIC PSEUDO-OBSTRUCTION IN PATIENTS WITH SEVERE TRAUMATIC INJURIES

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Background: Acute colonic pseudo-obstruction (ACPO) is characterised by acute large bowel dilatation without mechanical obstruction. We aim to evaluate patients with severe traumatic injury with respect to their response to treatment, and compare them to non-trauma patients.

Methods: A retrospective cohort study of patients who were treated for pseudo-obstruction in at a Level 1 trauma centre. Patient details were retrieved from a hospital-based computer system and patient notes. Management was determined by the treating surgeon. Both trauma (T) and non-trauma (NT) patients were given a trial of conservative management. Failing this they were managed with either neostigmine, colonoscopic decompression, or a combination of both.
Results: A total of 41 cases were identified from 2008-2012, 20 trauma and 21 non-trauma patients. Conservative management was successful in 35% (T) and 29% (NT). In the non-trauma group, the success rate for colonoscopy and neostigmine were 90% and 100% respectively. Trauma patients experienced a poorer response to treatment with 8 patients requiring repeat interventions, compared to 3 in the non-trauma group (40% (T) vs 14.3% (NT), p=0.063). Neostigmine overall was less successful in the trauma patient (75% (T) vs 100% (NT), p=0.043). Single colonoscopy was successful in 28% (T) vs 80% (NT) of patients (p=0.03). 4 out of 5 trauma patients receiving neostigmine after partial response to colonoscopy resolved (80%). There were two colonic perforations in each group.

Conclusion: ACPO is more difficult to treat in patients with severe traumatic injury likely due to the ongoing sympathetic hyperactivity in trauma. Colonoscopic decompression is equally as effective as neostigmine in non-trauma patient. In the trauma patient, colonoscopic decompression alone is less effective than neostigmine or colonoscopy plus neostigmine. We suggest a more aggressive approach to managing ACPO in patients with severe traumatic injury. Multiple interventions are often required to achieve resolution in the trauma cohort.

116 DR ANGELIKA NA

LAPAROSCOPIC VERSUS OPEN ULTRA-LOW ANTERIOR RESECTION: COMPARISON OF SHORT-TERM COMPLICATIONS

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Purpose: Laparoscopic assisted ultra-low anterior resection (Hybrid ULAR) for rectal cancer is increasingly accepted as an alternative to open surgery. This study evaluated the complications associated with laparoscopic and open approaches.

Methods: 94 patients who underwent elective laparoscopic or open ULAR or abdomino-perineal resection between 2003 -2009 were identified from the hospital colorectal cancer database. Demographics, operative details, postoperative complications and recurrence were retrospectively collected from medical records.

Results: There were 31 lap (L), 4 lap converted to open (C) and 63 open (O) surgeries. The rate of postoperative complications was higher in the open surgery group (C and O) (41.8%) compared to the lap group (25.9%) (p<0.001). There were 2 anastomotic leaks in the C group. (compared to 0 in L and C 3.8%) (p<0.003). The incidence of wound infection was in C (25%), followed by O (18.3%) and L (0%) (p<0.003). However, the difference in the rate of superficial infection in C (5%), O 8.3% and L 3.8% (p<0.032), deep wound dehiscence (C 0%, O 1.6%, L 3.8%) (p<0.043) and septicaemia (C 25%, O 26%, L 19.2%) were not statistically significant. The rate of prolonged ileus was 25% in C, 8.3% in O and 3.8% in L (p<0.212). The rate of small bowel obstruction was higher in O (5%) compared to L (3.8%) cases (p<0.081).

Conclusion: The overall postoperative complications, in particular the anastomotic leak rate was significantly higher in open compared to the laparoscopic surgery group. There was also a trend towards higher rate of wound dehiscence, prolonged ileus and small bowel obstruction in lap converted to open and open surgery patients.

117 DR KARY SUEN

IMPACT OF AN ACUTE GENERAL SURGERY SERVICE ON THE OUTCOMES OF APPENDICECTOMY

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Introduction: Appendicectomy is a common general surgical emergency procedure and can therefore be used as a surrogate marker to evaluate quality in surgical management. The aim of this study was to assess the outcomes of appendicectomy before and after the introduction of the consultant led Emergency General Surgery (EGS) service at a large metropolitan tertiary referral centre.

Methods: A retrospective historical control study was performed which included all adult patients undergoing appendicectomy during two 18 month periods, before and after the introduction of the EGS service. Data collected included patient demographics, use of radiological investigations, time to surgery, length of hospital stay and histopathology. Outcome measures were time to surgery, hospital length of stay, use of radiological investigations, negative appendicectomy rate (NAR) and perforation rate.

Results: The EGS service resulted in an increase in time to surgery without increase in length of hospital stay. There was an increase in appendicectomies performed within office-hours (64.4% vs 54.3%, p<0.01) without a significant increase in NAR or perforation rates (15% and 5.6% respectively). Computed Tomography (CT) imaging was reduced from 38.4% to 26.6% (p<0.01).

Discussion: The introduction of a consultant led emergency general surgical service has resulted in a statistically significant decrease in CT scanning and greater proportion of appendicectomies performed within office hours without increase in length of stay. This has been without significant differences in the overall negative appendicectomy rate and perforation rate.
Conclusion: Outcomes may improve further with funding for designated emergency theatre access.

**FAST TRACK SURGERY AT THE ROYAL MELBOURNE HOSPITAL**

**YEN, A. Shedda, S**

**Introduction:** International data and current literature strongly support Enhanced Recovery After Surgery (ERAS) as a means of fast tracking colorectal surgery patients. It is achieved through a combination of patient education minimally invasive surgery and deliberate surgical decisions. We are initially determining factors which influence the patient pathway from preadmission clinic to discharge.

**Methods:** Patients were recruited with ethics approval. Patients from the colorectal units were pooled together from 4 surgeons. They were analyzed according to BMI, use of bowel prep, laparoscopic vs open surgery, use of nasogastric tube and days to light ward diet. Any post operative complications were noted.

**Results:** Of the 40 patients recruited, the average BMI was 25.9. 14 cases were performed laparoscopically, two were converted to open, 13 were open and the remainder through parastomal incision. 50% had bowel prep. 24 patients did not require NG tubes. As a collective group, the mean days to flatus was 2.4 (Range 1-5 days), days to bowel movement was 3.9 (Range 2-7 days), days to ambulation 5.2 (range 1-22 days), days to light ward diet 3.3 (range 0-8 days) and the mean length of stay was 8.5 (range 1-23 days). Whilst days to light ward diet were associated with days to bowel movement, time for bowel movements was not associated with LOS. Instead, the LOS is significantly associated with days to ambulation, p = 0.007.

**Discussion:** Gathering the data requires detailed recording of each criteria investigated. The traditional association between days to flatus or bowel movement and LOS was evident. Length of stay was mainly due to the difficulty with mobility which we are currently investigating whether this is due to pre-operative morbidity. We will also be developing strategies to improve mobility post-operatively. Other strategies include investigating the association between mode of analgesia and days to ambulation, and thereby, the length of stay.

**Conclusion:** We have identified some of the factors related to length of stay for colorectal patients and potential barriers to the implementation of an ERAS program.

**THE RELIABILITY OF READINGS BY HOSPITAL STAFF WHEN USING COMMON SURGICAL DRAINAGE SYSTEMS**

**Yue BYT, Zhang C, Ting J, Nizzero D, van Zyl N**

**Introduction:** Wound drainage is an integral part of modern surgical practice and widely used in all surgical specialties. The decision to remove a drain is multifactorial but is strongly associated with the output over a 24-hour period. Therefore, accurate reading is required for clinical decision making. The aim of this study is to assess whether the commonly used drains could be read accurately by both nursing and medical staff.

**Method:** Three commonly used drainage systems, UnoVac®, RedonVac® and Jackson-Pratt® were filled with 10mls, 25mls, 40mls and 90mls of black tea respectively to represent serous bodily fluid. 38 nurses and 38 doctors were asked to estimate the drain volume with the result being documented by a blinded observer. For statistical analysis, a three-way analysis of variance (ANOVA) with repeated measures was performed, with significance level set to 0.05. Bonferroni (post-hoc) correction was applied to all significant pairwise comparisons.

**Results:** Jackson-Pratt® system outperformed UnoVac® and RedonVac® systems at volumes >10ml. No consistent trend was found at volume of 10ml. No significant difference in accuracy between nurses and doctors were identified across all drainage systems. Volume measurements were significantly less accurate at higher volumes for both doctors and nurses.

**Conclusion:** Doctors and nurses are equally proficient in estimating drain tubes; This study suggests that Jackson-Pratt is the drainage system of choice; As accuracy of volume measurement is diminished at the extremes of drain volumes, regular emptying of drainage systems is recommended to avoid overfilling of drainage systems.

**OUTCOMES OF DECOMpressive CRANIECTOMY IN PATIENTS FOLLOWING TRAUMATIC BRAIN INJURY**

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We performed a retrospective audit the outcomes of decompressive craniectomy (DC) in patients following traumatic brain injury. A total of 57 patients who underwent DC at The Royal Melbourne Hospital from 1st January 2005 to 30th
June 2011 were included in the study. Patients had a median age of 30 years (17-73 years) and included 42 males (73.6%). Pre-operative imaging showed subarachnoid haemorrhage in 49 patients (86%) and midline shift more than 5mm in 22 patients (38.6%). Twenty-eight patients (49.1%) underwent a primary DC, while 29 patients (50.9%) had a secondary DC. Unilateral DC was performed in 24 patients (42.1%), while bilateral DC was done in 33 patients (57.9%). Evacuation of intracranial haematoma took place for 26 patients (45.6%). Twenty-seven patients (47.4%) died during hospital admission. A higher postoperative median ICP was the most significant predictor of hospital mortality (OR=1.24, 95%-CI=1.07-1.44).

There was a mean decrease of 7.7mmHg in ICP between the mean preoperative and postoperative intracranial pressure (ICP) values (95%-CI=10.5 to -5.0). Postoperative cerebral perfusion pressure (CPP) values were available for 26 patients. There was a mean decrease of 3.5mmHg in the mean CPP from preoperative to postoperative CPP values (95%-CI=-6.2 to -0.8).

According to the Extended Glasgow Outcome Scale (GOSE) measure of outcome at 6 months follow up, a poor outcome (GOSE 1-4) was seen in 39 patients (68.4%), while a good outcome (GOSE 5-8) was noted in 15 patients (26.3%). Follow up information was unavailable for three patients. A high APACHE II score on admission was the most significant predictor of worse GOSE at 6 months (OR=1.4, 95%-CI=1.12-1.73), while a high postoperative median ICP was also a significant predictor of worse outcome.

While DC did not result in an overall improvement in CPP, it did result in lower ICP postoperatively, which was correlated with better outcomes in patients. Further randomized controlled trials are needed to achieve Class I evidence for DC, and for further development of guidelines for the implementation of DC.

121  DR DAVID CANTY

ESTIMATION OF RIGHT AND LEFT ATRIAL PRESSURE USING ECHOCARDIOGRAPHY IN PATIENTS UNDERGOING CARDIAC SURGERY.

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Background: Left atrial pressure (LAP) and its surrogate, pulmonary capillary wedge pressure (PCWP), is important for determining left ventricular diastolic function. Assessment by transthoracic echocardiography (TTE) is currently the non-invasive gold standard but there are few data for anaesthetised or mechanically ventilated patients or by assessment with transoesophageal echocardiography (TOE). A reliable method for estimating LAP and PCWP in these situations is desirable as the current method of measurement of PCWP is pulmonary arterial catheterisation, which has lethal complications. The objective was to assess the correlation and accuracy of estimates of PCWP by TTE and TOE in patients undergoing cardiac surgery.

Methods: Twenty seven adult patients aged 63±10.5 years, undergoing on-pump coronary artery surgery were included after ethics approval and informed written consent. Exclusion criteria included emergency surgery, atrial fibrillation and more than mild regurgitation of the aortic or mitral valves. Simultaneous echocardiographic and invasive haemodynamic measurements (pulmonary artery catheter) were obtained prior to anaesthesia (TTE), after anaesthesia and mechanical ventilation (TTE and TOE), during conduit harvest (TOE), and after separation from cardiopulmonary bypass.

Results: Left ventricular fraction was low (<0.5) in 7 and normal in 20 patients. The only Doppler values that remained consistent over measurement periods were E/E’ and S/D ratios. However, good correlations with PCWP occurred only in patients with low EF prior to anaesthesia with TTE for E velocity, deceleration time, pulmonary vein D, S/D, and E/E’ ratios. After induction of anaesthesia correlations of Doppler with PCWP were poor using either TTE or TOE. In patients with normal ejection fraction, correlations were poor for all time periods and modalities. However, a fixed curve pattern of interatrial septum and S/D <1 predicted raised PCWP (PCWP≥16mmHg AUC 0.76 and 0.74, PCWP≥17 AUC 0.89 and 0.74, PCWP≥18 AUC 0.98 and 0.78 respectively).

Conclusion: The fixed curve pattern of the interatrial septum (TTE and TOE) was the best predictor of raised PCWP when the PCWP ≥ 17 mmHg. Doppler assessment with TTE and TOE showed insufficient correlation with PCWP to be clinically useful in anaesthetized and mechanically ventilated patients undergoing cardiac surgery.

122  DR PATRICK PREECE

PREDICTORS OF RE-PRESENTATION FOLLOWING EXTERNAL SHOCKWAVE LITHOTRIPSY

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BACKGROUND: External shockwave lithotripsy (ESWL) has been used as a non-invasive method of treatment for both renal and ureteric calculi since it was first developed in the 1980’s. Nonetheless, complications of the treatment can arise such as sepsis and steinstrasse, presenting as pain and haematuria. Of those who have an unexpected re-
presentation to hospital, 43% require intervention and severe sepsis occurs in 1%. Stone size is a well known predictor of subsequent complications, and ESWL is rarely employed unless calculi are less than 20mm in diameter. This study aims to determine whether other factors can be used to predict re-presentation following ESWL. Given the paucity of local publications examining ESWL outcome, this study will compare a regional centres experience with contemporary international standards.

**METHOD:** A retrospective analysis was performed on 104 consecutive patients who underwent ESWL in both the public and private hospital over the 2 year span from June 2010 to July 2012. Data was collected regarding patient demographics, stone size, stone location, number of stones, use of pre and post-operative ureteric stenting, antibiotic prophylaxis, re-presentation rates and nature of complications.

**RESULTS:** Of the 104 patients who underwent ESWL, mean calculus size was 8.77mm (5-17mm). Of these, 26% of patients (n=27) received treatment to multiple calculi. 9.6% of cases (n=10) had an unplanned re-presentation to hospital due to a post-procedure complication: 6 with pain, 2 with urinary retention, 1 with fever and 1 with severe sepsis. Of these, 40% presented within 24 hours. Operative intervention was required in 50% (n=5). Incidence of re-presentation was associated with a stone size greater than 10mm. RR= 4.27, 95% CI [1.18, 15.54], (p=0.03, Fisher’s Test). A logistic regression showing the probability of re-presentation increasing with larger stone size approached statistical significance (p=0.07). Incidence of re-presentation had an association with stone location approaching significance (p=0.09): Intrarrenal or pelviureteric stones were present in 100% of cases and 80% of controls. No statistical difference was demonstrated amongst other variables including number of stones, pre or post operative stenting and use of prophylactic antibiotics.

**CONCLUSION:** Calculus size greater than 10mm is associated with an increase risk of re-presentation. No other predictive factors were identified. Our experience in a regional centre is comparable with contemporary international standards.

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**123 DR JONATHAN BILMEN**

**THE USE OF ACTIVATED CHARCOAL FILTERS IN PATIENTS WITH MALIGNANT HYPERTHERMIA: A CHEAPER WAY?**

*BILMEN JG, Gillies R*

**Introduction:** Malignant hyperthermia (MH) is a life-threatening condition caused by exposure of susceptible individuals to volatile anaesthetics or suxamethonium. Volatile agents are used to anaesthetize most non-MH susceptible patients and thus anaesthetic delivery workstations are contaminated with a residual amount of volatile agent. MH susceptible individuals must avoid exposure to all volatile anaesthetic agents, so accurate and reproducible processes to remove residual anaesthetic agents are required. Activated charcoal filters (ACFs) have been used to remove residual volatile agents from anaesthetic workstations. Prior to their introduction, anaesthetic machines were primed with high flow oxygen flushing of clean anaesthetic circuits for up to 90 minutes. ACFs have reduced the time for preparing an anaesthetic machine for MH patients to 3 minutes. Currently, the only commercially available ACFs are the "Vapor-Clean" filters which retail at approximately $130 per set of 2, both of which are to be used concurrently in a circle system for each patient. The Royal Melbourne Hospital anaesthetises between 50 and 100 patients with MH per annum. ACFs could therefore add $13000 per year to the cost. We therefore decided to investigate if we could safely reduce the cost of using the filters by only utilising one filter per patient.

**Methods:** Anaesthetic machines were saturated with anaesthetic vapours and connected to a Miran ambient air analyser (SaphirRe XL) to measure vapour concentration. We tested various configurations of filters and scenarios in order to determine optimal time for preparing an anaesthetic machine for use and the cost incurred. We also tested the longevity of the filter when placed in a circuit.

**Results:** We found, that placement of filters in an unprepared circuit was insufficient to safely prepare an anaesthetic machine. Upon use of one filter alone on the inspiratory limb, we were able to safely prepare an anaesthetic circuit within 3 minutes, following flushing of the anaesthetic machine with high flow oxygen for 90 seconds and a circuit/soda lime canister change. In addition, a single filter was able to maintain a clean circuit for 12 hours, with gas flows dropped from 10 litres/min to 3 litres/min after 90 minutes or the filter could be removed after 90 minutes provided that high gas flows were maintained.

**Conclusions:** The use of a single ACF was sufficient in preparing an anaesthetic circuit for use in patients with known MH, reducing the cost of use of filters and significantly reducing preparation time of anaesthetic machines.

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**124 DR ANDREA BOWYER**

**A COMPARISON OF NEUROCOGNITIVE ASSESSMENT BATTERY FOR ASSESSING POCD VERSUS POST-OPERATIVE QUALITY OF RECOVERY SCALE (PQRS) TO ASSESS COGNITIVE RECOVERY IN PATIENTS UNDERGOING CARDIAC SURGERY**
Background: Postoperative recovery is complex and can be measured over multiple domains using the Postoperative Quality Recovery Scale (PQRS). This study assessed the sensitivity of detection, and predictive power, of PQRS in detection of Postoperative Cognitive Dysfunction (POCD).

Methods: 50 patients undergoing cardiac surgery were recruited in this single centre, observational study. PQRS assessed recovery in four domains (cognitive, nociceptive, emotional and activities of daily living (ADLs)), with recovery in each domain being defined as a patient’s return to baseline score (or better). Repeated measurement bias was reduced using parallel forms and a validated tolerance factor. Concurrent PQCD assessment was via a formal 14-point neurocognitive test. Comparison was made at clinically significant timepoints of recovery as measured by PQRS (in all domains PQRS-ALL, in cognitive domain PQRS-Cog) and POCD.

Results: Construct validity was confirmed as incident patient recovery increased with time (PQRS-ALL day 3-5 19%, week 6 68 44%; POCD day 3-5 25%, week 6 62%). POCD incidence at week 6 was also consistent with that observed in the study institution. PQRS-ALL and PQRS-Cog both had a sensitivity of 82% in excluding POCD at 3-5 days, with PQRS-Cog having a 95% sensitivity at week 6 and a NPV for POCD recovery of 80% at day 3-5. Similarly, recovery in PQRS-ALL at day 3-5 had a PPV of 78% with respect to the absence of POCD at week 6-8. Recovery in PQRS-Cog at multiple timepoints was highly sensitive for the absence of POCD at 6-8 weeks (sensitivity PQRS-Cog day3 82%, day 14 81%, day 30 81%). Similarly, recovery in PQRS-ALL at multiple time points was highly specific for the absence of POCD at 6-8 weeks (specificity PQRS-ALL day 3-5 88%, day 14 71%, day 30 70%).

Conclusion: PQRS-ALL and PQRS-Cog were sensitive in detection of POCD at day 3-5 and Week 6-8 respectively. A recovery in PQRS-Cog at early postoperative timepoints (day 3-5, day 14 and day 30) was suggestive of the absence of POCD at week 6-8, with concurrent failure of recovery in all PQRS suggestive of POCD development. Furthermore, a recovery in PQRS-ALL at day 3-5 was predictive of no POCD at week 6-8. These results indicate that the PQRS, and in particular its cognitive domain, is reliable in detection and prediction of POCD which may enable the identification of patients at higher risk of POCD early in the postoperative period such that intervention may be implemented.

THE VENNER A.P. ADVANCE LARYNGOSCOPY SYSTEM: A COMPARISON OF THE DIRECT AND VIDEO-ASSISTED LARYNGEAL VIEWS OBTAINED DURING ROUTINE AIRWAY MANAGEMENT.


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The evolution of videolaryngoscopy (VL) remains a burgeoning field of anaesthetic research and has resulted in the commercial release of multiple videolaryngoscopes (VLS). These devices can be broadly classified as Macintosh-style (direct), 'Non line-of-sight' featuring an angulated laryngoscopic blade or VLS with a tube channel. The Venner A.P. Advance (APA) laryngoscopy system is a relatively new VLS which exhibits the functionality of all three classifications.

We evaluated the APA as both a direct and video-assisted laryngoscope.

The primary outcome measure was the overall Cormack and Lehane (CL) scores obtained by direct laryngoscopy and video-assisted laryngoscopy for all patients.

Methods: The requirement for informed consent was waived by our hospital ethics committee as this was a quality assurance study that did not expose patients to any additional procedure. We prospectively recruited patients scheduled for elective or emergent surgery that required orotracheal intubation. We recorded general patient characteristics as well as airway assessment features and any other predictors of difficult intubation. Laryngoscopy was performed by one of seven consultant anaesthetists, each of whom had performed at least ten prior laryngoscopies with the APA. Direct 'Macintosh-style' laryngoscopy was performed initially and the best glottic view obtained was recorded. At this point the viewing screen was applied to the handle and the APA was re-manipulated to obtain the best indirect glottic view on screen. Secondary outcomes included any association between the CL difference score and patient characteristics including airway assessment parameters. We also recorded the proportion of patients successfully intubated with the APA, the viewing modality used for intubation as well as the use of any intubation aids.

Results: 178 patients were included in this study over a six month period. Overall, the CL score obtained was significantly lower with videolaryngoscopy (VL) than with direct laryngoscopy (DL), p< 0.001. In 133 (75%) patients the view obtained with DL and VL was the same. In 40 (22.4%) patients the view was one or more grades lower with VL compared to DL. There were 2 patients in whom intubation with the APA was unsuccessful.

Conclusions: We demonstrated that the APA videolaryngoscope provides a better glottic view in both easy and difficult airways than that obtained when using it as a direct laryngoscope. Further comparative studies, incorporating the Difficult Airway Blade, are required to fully evaluate this promising device.
LARGE PERIOPERATIVE TRIALS IN ANAESTHESIA

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Millions of patients present for elective non-cardiac surgery every year worldwide and many are elderly and/or at risk of serious perioperative morbidity and mortality. Proven strategies to prevent these complications therefore could have a significant impact on health resource utilisation and patient quality of life.

The Department of Anaesthesia and Pain Management at the Royal Melbourne Hospital is currently engaged with four large multi-centre perioperative trials, which are funded by the NHMRC and endorsed by the Australian and New Zealand College of Anaesthetists Trials Group.

1. The ENIGMA-2 Study
This 7,000 patient trial, due for completion in 2013, is randomising patients to nitrous oxide-based or nitrous oxide-free anaesthesia and measuring 30-day death and major cardiovascular morbidity in older patients with or at risk of cardiovascular disease and presenting for major non-cardiac surgery.

2. The POISE-2 Study
This study is a collaboration with the Population Health Research Institute at McMaster University in Canada and is due for completion in 2013. 10,000 older patients with or at risk of cardiovascular disease and having major non-cardiac surgery are being randomised to aspirin and/or clonidine and/or match placebos in a factorial design. The primary endpoint is 30-day mortality and cardiovascular morbidity.

3. The Balanced Study
In this study, due to start soon, 6,500 older patients with significant co-morbidities having major surgery are being randomised to deep or light general anaesthesia as measured by bispectral index (EEG) monitoring. The primary endpoint is one-year mortality.

4. The RELIEF Study
Restricted versus liberal fluid administration in patients with significant co-morbidities presenting for major open abdominal surgery is the focus of this 2,800 patient trial which is due to start soon. The primary endpoint is one-year disability free survival.

AN ULTRASOUND NEEDLE INSERTION GUIDE IN A PORCINE PHANTOM MODEL

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Ultrasound is routinely used in anaesthesia to assist vascular access and regional anaesthesia, by helping to visualise the patient’s anatomy and the needle being used. However visualisation of the proceduralist’s needle can be difficult, potentially compromising patient safety. We investigated a needle guide that aims to improve needle visualisation.

We compared nerve blockade with and without the InfinitiTM needle guide in an ultrasound in-plane porcine simulation.

We recruited 30 anaesthetists with varying blockade experience. The needle tip was visible less without than with the guide, median (IQR[range]) percentage time 23% (13–43 [0–80]) vs 67% (56–81 [29–100]), p < 0.001. The needle tip was invisible 25 (9–52 [1–198]) vs 2 (1–4 [0–19]) s, respectively, p < 0.001. The corresponding block times were 32 (15–67 [5–225]) vs 8 (6–10 [3–28]) s, p < 0.001. The needle guide reduced the block time and the time that the needle was invisible, irrespective of anaesthetist experience. This improves efficiency and may improve safety of procedures using ultrasound guidance for regional anaesthesia and vascular access.

THE UNIVERSITY OF MELBOURNE AND RESEARCH IN ANAESTHESIA, PERIOPERATIVE AND PAIN MEDICINE

STORY DA
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Australia and New Zealand are world leaders in research in Anaesthesia, Perioperative and Pain Medicine; per capita we are THE leaders. Hospitals affiliated with the University of Melbourne play an important role in this research which in 15 years has led Anaesthesia from being unrecognised at the NHMRC to having the highest ranked NHMRC project grant in 2012. The key to this success has been collaboration. To further enhance multicentre research (and teaching) the University of Melbourne has appointed a Professor and Chair of Anaesthesia.
BACKGROUND: While arthroscopies have commonly been used to treat knee osteoarthritis (OA), evidence over the past decade has shown these procedures have limited clinical benefit compared to conservative management (exercise, simple analgesia, weight loss).

METHODS: Semi-structured telephone interviews were conducted with 33 participants across Australia who were randomly selected from the larger cross-sectional survey (N=1157). The survey sample was drawn from the federal electoral roll and included people aged 39 years and over from all states and territories. The main themes covered in each interview included the journey from development of OA to more severe joint disease, willingness to undergo joint replacement surgery, and perceived enablers and barriers to accessing conservative and surgical treatment. QSR NVivo 10 software for the analysis of qualitative data was used to facilitate thematic analysis of the interview transcripts. Data coding was undertaken using themes arising from the interview data until no new themes emerged. A subset of interview transcripts was analysed by a second reviewer to confirm the themes identified and identify any important omissions.

RESULTS: Participants reported a range of barriers to accessing conservative and surgical treatments. These included not having private health cover, difficulty in taking time off work for appointments or post-operative recovery, the costs associated with treatment, challenges in obtaining referrals to specialists, and lengthy waits for appointments with health professionals. A further theme was patient concern about the inability of some health professionals to help with their OA and frustration with a perceived lack of effective treatments. A number of participants also reported that their doctor considered they were too young for joint replacement surgery or that surgery should be saved for later. For some, this seemed at odds with their current level of pain or friends’ experiences of joint replacement, suggesting that the reasons for delay are not being appropriately explained to patients.

CONCLUSIONS: People with hip or knee OA may experience a range of barriers to receiving appropriate care, and these included financial, personal and health system-related challenges, and medical attitudes regarding the timing of surgery. Given the growing burden of OA in Australia, an improved understanding of access determinants will assist with improving health outcomes and equity of access to health care.
decreased substantially over time. The lack of explicit guidelines in Australia regarding the use of arthroscopic surgery in patients with OA may lead to differing thresholds for intervention and geographical variation in procedures rates.

Aims: To evaluate the frequency and geographical variation in knee arthroscopy procedures for adults aged 25 years and older with a concomitant diagnosis of osteoarthritis in the state of Victoria, Australia over a one year period.

Methods: We analysed a retrospective, cross-sectional cohort of hospital separations involving an elective knee arthroscopy for patients with a primary or associated diagnosis code indicating osteoarthritis (OA) using routinely collected public and private hospital data from 1 July 2008 to 30 June 2009. Records were excluded if the patient was under 25 years or their arthroscopy involved a ligament reconstruction. Data on the estimated resident population in each health service region by age and sex was obtained from the Victorian Population Health survey for the 2008/09 financial year. The main outcome measure was the age and sex-adjusted incidence rates and variation by health service region.

Results: Over the study period, there were 9,849 arthroscopic procedures meeting the inclusion criteria. The majority of procedures were arthroscopic meniscectomies (6,278, 63.7% of all procedures) followed by arthroscopic debridement of the knee (846, 8.6% of procedures). After stratification by age and gender (Figure 2), the Grampians region had the highest rate of arthroscopies in the 45-64 year old age group at 819 arthroscopies for males and 772 for females per 100,000 population. The lowest rate in this age group was in the Southern metropolitan region which had 332 and 333 per 100,000 population for males and females, respectively.

Conclusions: We identified considerable geographical variation in arthroscopies for people with OA across the Victorian health service regions, particularly in regional areas. Further investigation is needed to understand whether this variation is a reflection of differences in prevalence of OA and its risk factors or surgical practices in the regions.

131 MS BERNARDA CAVKA

'CLOSING THE LOOP': EVALUATION OF THE OSTEOARTHRITIS HIP AND KNEE SERVICE

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Background: The Osteoarthritis Hip and Knee Service (OAHKS) was implemented at The Royal Melbourne Hospital (RMH) in 2006 to improve the management of patients with osteoarthritis through evidence based multidisciplinary management and more effective prioritisation of joint replacement surgery. Anecdotally, there has been a positive response from patients, clinicians and executive management following implementation of the OAHKS at RMH; however, a comprehensive evaluation of the OAHKS has not been undertaken. This project aims to: 1. Evaluate the impacts and outcomes of the OAHKS; and 2. Evaluate whether the OAHKS has been implemented as planned in relation to initial goals, and explore any barriers to implementation.

Methods: 1. Comparison of systematically collected patient and waiting time data from 2003-2006 (pre-OAHKS implementation) and 2006-2012 (post-OAHKS implementation). Data will be extracted from a research dataset, the OAHKS database, orthopaedic unit database, and medical records. 2. Development of a program logic model to enable program evaluation. 3. Focus groups and semi structured interviews involving participants as listed below. 4. Benchmarking components of the Melbourne Health OAHKS model with other primary and chronic care models. Patients and stakeholders will be invited to participate in the study including: 1. Patients referred to RMH for management of hip and / or knee OA (approximately 30 patients will be selected based on gender, age, joint affected, and appointment type (initial visit and follow-up)). 2. Members of the original and current project teams involved in the development and implementation of the OAHKS across Victoria. 3. Managers and clinicians working across the OA and joint replacement surgery continuum of care at RMH. 4. General practitioners and local community health care providers.

Expected outcomes: The project will enable us to evaluate whether the OAHKS model has been implemented as intended and whether project aims have been met, namely to improve access to orthopaedic care, prioritisation for joint replacement surgery and to facilitate conservative care for people with OA. The evaluation process will also enable formal feedback about the service to be given to key stakeholders and consumers. If the OAHKS is found to be an effective model of care, this could lead to further expansion of this model in the management of patients with other chronic diseases.

132 DR JOHN MOI

RETINAL VASCULAR CALIBRE MEASUREMENTS REMAIN STABLE OVER TIME IN RHEUMATOID ARTHRITIS PATIENTS WITH LOW DISEASE ACTIVITY

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BACKGROUND. Retinal vascular calibre (RVC) measurement is a non-invasive test which reflects the cumulative effects of cardiovascular (CV) risk factors and inflammation and can predict incident CV disease. We have previously demonstrated abnormal RVC (widened venular calibre) in rheumatoid arthritis (RA) patients, particularly those with high disease activity. We hypothesise that suppression of inflammation will result in normalisation of widened retinal venular calibre and are currently testing this hypothesis. The present study is a complementary evaluation of the longitudinal stability of RVC measurements in RA patients with stable, low disease activity.

AIM. To investigate the longitudinal stability of RVC measurements in RA patients with low disease activity receiving stable immunosuppression.

METHODS. Twenty-five RA patients with DAS-28-CRP scores <3.2 underwent retinal photography at baseline and 3-months later. Images were analysed by a trained assessor blinded to subject identity and timing of retinal photography. Summary measurements of retinal vessel diameter were provided as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE). Pairwise comparisons of RVC measurements between baseline and follow-up were performed using the paired t-test.

RESULTS. The RA patients (mean±SD age 53±9.5 years) were predominantly female (80%), with a mean±SD disease duration of 10.5±9.3 years. Disease activity remained stable (DAS-28-CRP score <3.2) over the study period (data not shown). No significant change was identified in the RVC measurements of RA patients between baseline and 3 month follow-up for CRAE (mean difference 0.46µm; 95% confidence interval -1.95 to 2.86µm, p=0.70) or CRVE (mean difference 2.73µm; 95% CI -5.93 to 0.48 µm, p=0.09).

CONCLUSION. This study suggests that RVC measurements remain unchanged during short-term follow-up of RA patients with stable, low level systemic inflammation. It provides a useful comparison for our concurrent longitudinal study investigating the effect of potent immunosuppression on serial RVC measurements in RA patients with high disease activity.

133 MISS REEM SALEH

COLONY-STIMULATING FACTOR-1 AND TUMOR NECROSIS FACTOR- A IN ARTHRITIC PAIN

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Colony-stimulating factor-1 (CSF-1) is a key cytokine that has been linked to the development of arthritis in animal models. Its role in neuropathic pain has been studied by several laboratories; however, its potential involvement in arthritic pain has not received attention. Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine which has been implicated in the pathogenesis and progression of RA, as well as the generation of pain. Thus, the objectives of the current study were as follows: 1) to examine the role of CSF-1 in arthritic pain using an acute monoarticular methylated bovine serum albumin (mBSA)-induced arthritis model; 2) to compare the TNF-mediated pain to the CSF-1-induced pain; and 3) to elucidate the mechanisms by which CSF-1 can mediate arthritic pain. Results from this study showed that systemic administration of CSF-1 can induce pain in the mBSA model. Preliminary data showed that early CSF-1-induced pain was not reversed following indomethacin administration, suggesting that CSF-1-mediated pain is cyclooxygenase-independent. Systemic administration of TNF-α could also induce pain in the novel mBSA model. Unlike CSF-1, early TNF-mediated pain was abolished following the administration of indomethacin. This indicated that the TNF-mediated pain is mediated through the production of eicosanoids. Thus, both cytokines were able to induce pain; however, each cytokine mediated arthritic pain via a different pathway. Further insight into the mechanisms by which CSF-1 mediates pain could determine its contribution to arthritic pain and may provide novel therapeutic strategies for joint pain.

134 MS JOANNE TROPEA

CARDIOVASCULAR EVENTS AND MORTALITY FOLLOWING JOINT SURGERY IN PATIENTS WITH AUTOIMMUNE RHEUMATIC DISEASE

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Introduction: Autoimmune rheumatic diseases (AIRD), such as rheumatoid arthritis, are associated with an increased risk of cardiovascular disease compared with the general population. There is limited information about the risk of cardiovascular (CV) events and/or death following surgery among people with AIRD.

Aims: To compare 6 week and 1 year CV event and mortality following joint surgery in AIRD patients compared with the general population.

Methods: Individuals who had undergone joint surgery in Victoria between 1 July 2000 and 30 June 2007 were identified from hospital discharge data. Individuals were classified as having AIRD using International Classification of Diseases, 10th Revision, Australian Modification classification codes recorded at the time of joint surgery or any hospitalisation during the previous 2 years. Incidence of CV events (defined as myocardial infarction, angina or stroke)
and/or mortality within 6 weeks and 12 months of joint surgery were determined from hospital data and linked death registry data. Bivariate analysis followed by logistic regression analyses were performed with AIRD as the key exposure variable. Covariates included in the adjusted models were age, gender, comorbidities (including hypertension, hyperlipidaemia, diabetes, pulmonary disease, renal disease and smoking), socioeconomic status, ethnicity, proximity to goods and services, admission type and patient type. Adjusted odds ratios (ORs) and 95% confidence intervals are presented.

Results: A total of 308,589 joint surgery episodes occurred among 240,571 individuals. 4637 (1.50%) episodes occurred among patients with AIRD, of which 3654 (1.18%) had rheumatoid arthritis. In adjusted logistic regression models the OR for CV event within 6 weeks in AIRD patients was 1.16 (95% CI 0.88-1.53) and death within 6 weeks in AIRD patients was 1.35 (95% CI 0.86-2.12). The adjusted OR for CV event within 12 months in AIRD patients was 1.38 (95% CI 1.17-1.63) and death within 12 months in AIRD patients was 1.92 (95% CI 1.55-2.38).

135 DR SHARON VAN DOORNUM

TIME TO INSTITUTION OF DMARD THERAPY IN EARLY RA – A FOLLOW UP STUDY AT ROYAL MELBOURNE HOSPITAL

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Aim: Early introduction of disease-modifying anti-rheumatic drugs (DMARDs) has been shown to reduce joint destruction and long-term disability in rheumatoid arthritis (RA). A previous audit of time from symptom onset to commencement of DMARD in early RA patients seen at RMH between 2002 and 2004 revealed a median delay of 386 days. Various measures were subsequently implemented in an attempt to reduce this delay. The aim of the present study was to re-examine this issue in a more recent cohort.

Methods: Patients referred to RMH with early RA and seen between January 2008 and October 2012 were identified via departmental records. The medical charts were reviewed and if necessary the local doctor was contacted for additional information. Data recorded included dates of symptom onset, initial GP consultation, referral to rheumatologist, rheumatologist review and commencement of DMARD. Serologic status and first DMARD commenced were also recorded.

Results: Thirty six patients (53% female, mean±SD age 58±16 years) were identified and contributed data. 72% (n=26) of patients were either RhF or ACPA positive. The median time from symptom onset to initiation of DMARD therapy was 160 days (range 28-2504). The median time from referral to clinic appointment was 31 days (range 2-136), and from clinic appointment to DMARD commencement was 21 days (range 0-217). The major component of the delay comprised the time from symptom onset to referral to the clinic, for which the median duration was 88 days (range 2-2434). ACPA positive status resulted in more rapid commencement of DMARD therapy (median 12 vs 35 days, p=0.078). The first DMARD commenced was methotrexate monotherapy in 56% (n=20) of patients.

Conclusions: These data reflect that while there has been improvement in time to DMARD institution in early RA at RMH, there are still considerable delays at every stage of the process.

136 DR BHASKER AMATYA

MULTIDISCIPLINARY REHABILITATION IN WOMEN FOLLOWING BREAST CANCER TREATMENT: A RANDOMIZED CONTROLLED TRIAL

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Background: Breast cancer (BC) is a major cause of morbidity and mortality, and the most common malignancy in women worldwide. The rehabilitation model presents opportunities for intervention throughout the disease continuum phases. The aim of this study was to assess the effectiveness of a multidisciplinary (MD) ambulatory rehabilitation programme for women following definitive BC treatment in an Australian community cohort.

Methods: Eighty-five women in the community were randomized to a treatment group (n=43) for individualized high intensity MD rehabilitation programme, or a control group (n=42) comprising usual activity. The MD rehabilitation programme was individualized, functional goal oriented with active patient participation, and included treatment beyond symptomatic management of BC, education to improve ‘activity’ and ‘participation’ within the limits of disease. The treatment programme included up to 3 one-hour sessions of interrupted therapy/week for up to 8 weeks, involving all relevant disciplines (Social, Psychology, Occupational Therapy and Physiotherapy) based on participants’ need and treating team’s consensus. The primary outcome Depression, Anxiety Stress Scale (DASS) scale measured restriction in ‘participation’. Secondary measures included Perceived Impact Problem Profile (PIPP) and
137 DR BHASKER AMATYA

FACTORS ASSOCIATED WITH LONG-TERM FUNCTIONAL OUTCOMES, PSYCHOLOGICAL SEQUELAE AND QUALITY OF LIFE IN PERSONS AFTER PRIMARY BRAIN TUMOUR

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Background: Primary brain tumour, a diverse group of neoplasms, accounts for approximately 2% of all cancers. Overall incidence of primary brain tumour is increasing. In recent years, therapeutic advances have prolonged survival rates. Despite these treatment options, brain tumour survivors often have residual neurological deficits, functional and psychosocial sequelae, which limit everyday activity and participation. The aim of the study was to examine factors impacting long-term functional outcomes and psychological sequelae in persons with primary brain tumours in an Australian community cohort.

Methods: Participants (n=106) following definitive treatment for brain tumour in the community were reviewed in rehabilitation clinics to assess impact on participants’ current activity and restriction in participation, using validated questionnaires: Functional Independence Measure (FIM), Perceived Impact Problem Profile (PIPP), Depression Anxiety Stress Scale, Cancer Rehabilitation Evaluation System—Short Form and Cancer Survivor Unmet Needs Measure.

Results: Mean age of the participants was 51 years (range 21-77 years), majority were female (56%) with median time since brain tumour diagnosis 2.1 years and a third (39%) had high grade tumours. Majority showed good functional recovery (median motor FIM score 75). Over half reported pain (56%), of which 42% had headaches. Other impairments included: ataxia (44%), seizures (43%); paresis (37%), cognitive dysfunction (36%) and visual impairment (35%). About 20% reported high levels of depression, compared with only 13% in an Australian normative sample.

Conclusion: Rehabilitation can benefit participation in BC survivors. Evidence for specific rehabilitation interventions is needed. Integrated cancer programmes allow opportunities to evaluate patients in various settings, but require outcome research to develop service models for survivorship issues.

138 DR BARBARA MURPHY

IMPROVED CARDIAC RISK AFTER PARTICIPATION IN THE BEATING HEART PROBLEMS SELF-MANAGEMENT PROGRAM: RESULTS OF A RANDOMISED CONTROLLED TRIAL WITH CARDIAC PATIENTS

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Purpose. While behaviour change can improve risk factor profiles and prognosis after an acute cardiac event, patients need assistance to achieve sustained lifestyle changes. We developed the ‘Beating Heart Problems’ cognitive behaviour therapy and motivational interviewing program to support patients to develop behavioural and cognitive self-management skills. This paper reports on the results of a randomised controlled trial of the program.
Methods. Patients (N=275) consecutively admitted to the Royal Melbourne Hospital and Melbourne Private Hospital after acute myocardial infarction (32%) or for coronary artery bypass graft surgery (40%) or percutaneous coronary intervention (28%) were randomised to treatment (T; n=139) or control (C; n=136) groups. T group patients were invited to participate in the 8-week group-based program, based at the RMH. Patients underwent risk factor screening six weeks after hospital discharge (prior to randomisation) and again four and 12 months later. At both follow-ups, T and C groups were compared on two-year risk of a recurrent cardiac event and key behavioural outcomes, using both intention to treat and ‘completers only’ analyses.

Results. Patients ranged in age from 32-75 years (mean=59.0; SD=9.1). Most (86%) were male. Compared with C group patients, T-group patients tended towards greater reduction in two-year risk, at both the 4-month and 12-month follow-ups. Significant benefits in dietary fat intake and functional capacity were also evident.

Conclusions. The ‘Beating Heart Problems’ program showed modest but important benefit over usual care at four and, to a lesser extent, 12 months. In order to extend its reach to cardiac patients throughout Australia, the ‘Beating Heart Problems’ program has been translated into an internet-based program titled ‘HeLP Yourself Online’.

139 MR JIANXIONG CHAN

DEVELOPMENT OF NOVEL POINT-OF-CARE TESTING FOR HLA-B*15:02

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Background: Screening for HLA-B*15:02 is recommended prior to starting carbamazepine in Han Chinese and Southeast Asians because the allele is strongly predictive of severe cutaneous adverse drug reactions to carbamazepine. However, conventional laboratory-based testing is inconvenient, time consuming and expensive, hampering its efficient application in clinical practice. We aim to develop a novel genotyping technology which sets as a foundation for the development of a low cost, fast and reliable point-of-care genotyping device.

Methods: HLA-B region containing the variations region of the gene will be amplified using a rapid isothermal amplification method known as loop-mediated isothermal amplification (LAMP). A detection system using DNA hybridisation of target DNA product with specific oligonucleotides complementary to HLA-B*15:02 region on silicon surface will be developed.

Result: LAMP is able to effectively amplify the target DNA region within 30 mins. The product was confirmed with sequencing to be the region of interest.

For detection system development, specific fluorescent target DNA product was observed to bind to the silicon surface with specific oligonucleotides complementary to HLA-B*15:02 region at 44oC. This suggested that 44oC will be a suitable temperature for specific DNA detection.

Conclusion: These results form the foundation for detection of HLA-B*15:02 on silicon nanowire which can in turn be developed into a low cost, fast and reliable point-of-care genotyping device. This technology can be readily adaptable to detect other DNA variants of interest for disease diagnosis.

140 MS MAIRA KENTWELL

AN EXPLORATION OF THE LIVED EXPERIENCES OF HAVING BRCA1/2 PREDICTIVE TESTING TOGETHER WITH A SIBLING.

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This study was carried out to explore the lived experiences of individuals who have had pre-test and post-test genetic counselling for BRCA1/2 predictive testing together with a sibling. The purpose of this study was to gain a better understanding of the experience of joint genetic counselling for siblings who had BRCA1/2 predictive testing together and to ascertain whether being consulted together met their needs and expectations.

The study design utilised a qualitative approach, with a phenomenology theoretical framework. Data was collected using one-on-one in-depth interviews and analysed using an interpretative phenomenological approach. Six participants who have had BRCA1/2 predictive testing with their sibling were recruited from the Royal Melbourne Hospital Familial Cancer Centre, Melbourne.

For this group of participants, the experience of attending together for genetic testing was a positive and beneficial one. Participants reported that they generally were not influenced by their sibling in their decision to have testing or to attend together. Their reasons for attending together were mainly based on practical or logistical considerations. In hindsight, participants identified numerous types of support that they were able to provide and receive from one another throughout the duration of the genetic testing process. Participants were highly satisfied with the joint
genetic counselling they received and explained that their needs and expectations were evenly addressed. They recommended genetic counsellors should provide the option to see siblings together for BRCA1/2 predictive testing. This is the first known study specifically seeking to understand the issue of siblings undergoing predictive genetic testing together. This study presents preliminary evidence that will assist in informing the genetic counselling practice when siblings request to be seen together for BRCA1/2 predictive testing.

141 DR STACEY PETERS

FAMILIAL CARDIAC EVALUATION IN SUDDEN UNEXPLAINED DEATH AND ABORTED CARDIAC ARREST SYNDROMES: THE ROYAL MELBOURNE HOSPITAL EXPERIENCE

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Introduction: We sought to evaluate the diagnostic yield of targeted cardiac and genetic testing for inherited arrhythmia syndromes in families of patients with sudden unexplained death (SUD) or aborted cardiac arrest (ACA).

Methods: 121 consecutive families (88 SUD, 33ACA), including 523 individuals (413 SUD relatives, 110 ACA probands and relatives) underwent evaluation. Cardiac testing included 12 lead ECG, exercise testing and echocardiography, in addition to holter, cardiac MRI and provocation testing if indicated. Targeted genetic testing was performed based on the results of the initial cardiac evaluation. SUD victims with evidence of structural heart disease on autopsy were excluded.

Results: Mean age of SUD was 26±15 (40% female) and ACA 30±16 (27% female). A clinical diagnosis of an inherited arrhythmia syndrome was established in 14 SUD families (16%) (Fig A). The most common diagnosis was long QT (LQT) syndrome (11/14). Of those with a clinical diagnosis, gene testing was performed and positive in 4 families (2-LQT1, 2-LQT2). In contrast, a clinical diagnosis was established in 19 ACA families (58%) (Fig B). The most common diagnoses were LQT syndrome (6) and Brugada syndrome (7). Of those with a clinical diagnosis 6 families (43%) had a positive genetic test (2-LQT1, 1-LQT2, 1-LQT3).

Conclusion: In contrast to published experience from smaller series, detailed cardiological and genetic evaluation in SUD families is of low diagnostic yield for inherited arrhythmia syndromes (16%). However DNA testing of SUD probands may improve yield. Diagnostic yield in ACA families was 4 fold higher (58%) consistent with published experience.

142 DR DAVID PATTISON

QUANTITATIVE ASSESSMENT OF THYROID-TO-BACKGROUND RATIO IMPROVES THE INTER-OBSERVER RELIABILITY OF 99MTC-SESTAMIBI THYROID SCINTIGRAPHY FOR INVESTIGATION OF AMIODARONE-INDUCED THYROTOXICOSIS.

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BACKGROUND: Amiodarone-induced thyrotoxicosis (AIT) is caused by excessive hormone synthesis and release (AIT I), a destructive thyroiditis (AIT II), or a combination of both (AIT Ind). No gold standard diagnostic test is available, however use of 99mTc Sestamibi Thyroid Scintigraphy (99mTc-STS) was recently described as an accurate tool for differentiating subtypes. This has important therapeutic implications as AIT I, AIT II and AIT Ind are managed with carbimazole, prednisolone, or combination therapy, respectively. However, the information available to guide reporting of 99mTc-STS is qualitative and highly subjective. This study aims to compare the inter-observer reliability of 99mTc-STS before and after use of quantitative thyroid-to-background ratios (TBR) displayed on a time-activity curve for differentiation of AIT subtypes.

METHODS: An audit of nuclear medicine departments at Royal Melbourne Hospital (Parkville, Vic) and Cabrini Hospital (Malvern, Vic) identified 15 consecutive 99mTc-STS studies performed for AIT. These studies were de-identified and re-processed with standardised background intensity. Four nuclear medicine physicians reported the studies according to previously established criteria (Series 1). Quantitative thyroid-to-background ratios (TBR) and estimated ‘normal’ range TBR were subsequently provided before the studies were re-ordered and reported again (Series 2). Inter-observer reliability was calculated using Fleiss’ kappa statistic (STATATM statistical software, Texas) for each assessment.

RESULTS: Diagnostic comparison. Series 1: Percentage Agreement (Median,[Range]): AIT I vs AIT Ind vs AIT II: 47%[47-63](Kappa 0.30); AIT I vs [AIT II & Ind]: 80%[67-87](Kappa 0.48); AIT II vs [AIT I & Ind]: 77%[60-87](Kappa 0.44); AIT Ind vs [AIT I & II]: 47%[47-73](Kappa -0.05). Series 2: Percentage Agreement (Median,[Range]): AIT I vs AIT Ind vs AIT II: 80%[73-80](Kappa 0.67); AIT I vs [AIT II & Ind]: 94%[87-100](Kappa 0.84); AIT II vs [AIT I & Ind]: 80%[73-93](Kappa 0.64); AIT Ind vs [AIT I & II]: 82%[73-93](Kappa 0.51).
Fleiss Kappa statistics assessing inter-observer reliability for each series of reporting and diagnostic comparison (Kappa < 0 poor agreement, 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, 0.81–1.00 almost perfect agreement).

CONCLUSIONS: 1. Use of quantitative thyroid-to-background ratio improves the inter-observer reliability of reporting 99mTc-STS for investigation of different types of AIT. 2. There is ‘almost’ perfect agreement upon differentiation of AIT I from AIT II and AIT Ind, with important implications for rationalizing use of corticosteroid therapy. 3. Prospective identification of AIT Ind is improved from ‘poor’ to a ‘moderate’ level of agreement to facilitate rational use of combination therapy at diagnosis.

143 DR STEWART MIDGLEY

MEASUREMENT OF ELECTRON DENSITY AND COMPOSITION USING DUAL ENERGY SYNCHROTRON COMPUTED TOMOGRAPHY AT 20-35 KEV

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A non-linear model for the x-ray linear attenuation coefficient μ was employed for dual energy x-ray analysis (DEXA) using the Canadian light source biomedical imaging beam line. The model characterizes materials by their electron density Ne and uses statistical moments to describe the distribution of elements using compositional parameters R which have the same “units” as atomic number.

DEXA measurements of μ are written as non-linear simultaneous equations, then solved for Ne and fourth compositional ratio R4. The method was tested using mono-energetic synchrotron computed tomography (CT) at 20-35 keV, with phantoms containing liquid samples of ethanol, water and salt solutions.

A fan beam geometry allowed the detection of forward scattered radiation with measurements being 6% lower than expectations for a narrow beam. Energy dependent model parameters were obtained by solving linear simultaneous equations formed by μ and material parameters based upon Ne and R4. Various noise sources were identified to give μ uncertainties of 1-2%. DEXA accuracy was studied as a function of model parameters, photon energy and composition. Propagation of errors analysis identified the importance of the fractional compositional cross-products whose difference at the two beam energies should exceed 0.1, requiring 10 keV or more separation. For a reasonable approximation of adjustable model parameters, the mean difference between DEXA solution and true values (ΔNe, ΔR4) are (1.0%, 0.5%) for soft tissue and (1.5%, 0.8%) for bone like samples.

The material parameters (Ne, R4) can be used to characterize the density and composition of materials. The model can be utilized in radiology, nuclear medicine and radiotherapy treatment planning to estimate tissue interaction parameters, for calculating nuclear medicine attenuation correction and radiation dose distributions at arbitrary photon energies. This study demonstrated DEXA at lower photon energies suitable for studying small animals and excised tissue samples. Further work will test the methodology at higher photon energies suitable for in-vivo large animal and human imaging.

144 RAYMOND WEN

RADIATION SCATTER IN THE OPERATING THEATRE

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Aims: We aimed to identify the areas of maximal scattered radiation exposure in the operating theatre relative to different techniques of image intensifier use. Our aims were to inform radiographers regarding the best position to reduce radiation exposure whilst screening in the operating theatre. A secondary objective was to inform theatre staff of the areas of highest radiation exposure.

Methods: We used 20cm of Perspex as a scatter medium to simulate the human body and measured radiation readings with a Geiger counter placed at differing distances and locations. Two image intensifier machines were tested with common angiographic and operative X-Ray modes and techniques tested.

Results: Standing behind the C-arm and control unit of the image intensifier machine provided the greatest reduction in scattered radiation exposure for the radiographer. Scattered radiation was highest next to the X-Ray tube, and using a non-standard technique with the X-Ray tube above the table significantly increased scattered radiation dose. Reflected angles resulted in higher scattered radiation, with lower scattered radiation exposure in the path of the directed beam. Newer technology provided by the pulsed fluoroscopic mode on a newer image intensifier reduced measured dose by a factor of 4.

145 MRS KELLIE LIERSCH
REDDUCING RECIDIVISM BY YOUNG ADULT OFFENDERS THROUGH THE PREVENT ALCOHOL AND RISK RELATED TRAUMA IN YOUTH PROGRAM (P.A.R.T.Y) WITH PSYCHOSOCIAL SUPPORT: A PILOT STUDY IN MELBOURNE

The Alfred Hospital, NTRI, Victoria Police, Sunshine and Werribee Magistrate Court, Youth Junction Inc.

The aim of this study is to assess the effectiveness of the Crimes Choices Consequences Program (CCCP) through recidivism rates.

The Crimes, Choices and Consequences Program (CCCP) targets young people aged 18-25 who appear in the Sunshine and Werribee Magistrates’ court. The youth attending are predominately male and have committed road safety violations. The program includes support from Victoria Police, Youth Junction Inc with the participants attending the Prevent Alcohol and Risk Related Trauma in Youth Program (P.A.R.T.Y). This program is a one day in hospital program conducted at The Royal Melbourne and Alfred Hospitals in which participants get to see first hand the reality of trauma and how choices and risk taking behaviours can have devastating effects.

A total of 346 young offenders participated in the CCCP and 125 of these completed the full 12 month program including follow up. Only 11 (8.8%) participants reoffended with the same or equivalent offence within 12 months and of these, 8 participants (72%) did so within 3 months of attending the P.A.R.T.Y program.

The results suggest that the CCCP is having a positive effect on reducing recidivism rates and that intervention programs such as this should be provided as early as possible in order to reduce early reoffending. However it is recognized that larger, prospective studies are required to further measure the impact of this program on recidivism.

146 MR STEVE HALPERIN

IMPROVING THE MENTAL HEALTH OF YOUNG PEOPLE IN OUT OF HOME CARE

Orygen Youth Health; Royal Children’s Hospital: Orygen Youth Health Research Centre; University of Melbourne.

Young people in out-of-home care have experienced a range of traumas and adversities. They are vulnerable to mental ill-health and associated problems with relationships, education and meaningful activity. Longer term they have higher rates of a range of mental health and substance use disorders, and are at greater risk of homelessness and other significant social problems. While these poor outcomes have been demonstrated repeatedly, mental health services in Victoria have been slow to respond.

This paper will describe a recently funded 5 year study which aims to develop an innovative approach to systematic and affordable delivery of effective mental health care responding to the needs of culturally diverse young people aged 12-17 years in OoHC (kinship care, foster care and residential care) in the North West region of metropolitan Melbourne. The study involves a collaboration between Orygen Youth Health, Royal Children’s Hospital and the Youth Support and Advocacy Service.

Stage 1 of the study will bring together young people, project partners and researchers and use a mixed methods approach to refine the proposed intervention and plan its implementation.

Stage 2 will continue the implementation and study the intervention effectiveness at three levels: with individual young people, with their carers and support workers and with the community agencies that support them. The interventions will build on the support that carers already receive by providing a training and consultation program with trauma informed, evidence-based practice elements across the service system. The aim is to develop cross-sector collaboration to reduce the risk of onset of mental ill-health and support more effective early intervention and treatment for mental disorders. The study plans to demonstrate that a helpful youth mental health prevention, early intervention and treatment response for young people in OoHC can be achieved with a relatively small re-allocation and redesign of existing resources. Such findings would have significant funding and policy implications for the intersection of the youth mental health and child protection sectors.

147 DR MARTA RAPADO-CASTRO

PREDICTIVE VALUE OF COGNITIVE FUNCTIONING OVER COPING STYLES ON PERCEIVED STRESS IN YOUNG PEOPLE WITH A FIRST EPISODE OF PSYCHOSIS

RAPADO-CASTRO M1,2,3, Allott KA1, Proffitt T-M1, Bendall S1, Garner B4, Butselaar F1, Phassouliotis C2, Markulev C1, McGorry PD1, Lin A5, Wood SJ 2,5, Cotton SM1, Phillips LJ6.
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Aims: Stress is implicated in the development and maintenance of psychotic illness. Understanding the factors that contribute to stress levels psychotic disorders will aid clinical assessment considerations and treatment targets. The aim of this study was to examine the impact of neuropsychological functioning and coping styles on level of perceived stress in people with first-episode psychosis (FEP). Method: Participants were 34 neuroleptic-naïve FEP patients, recruited from the Early Psychosis Prevention and Intervention Centre, Melbourne, Australia. Participants completed a battery of neuropsychological tests examining premorbid and current IQ, immediate attention, working memory, verbal learning and memory, verbal fluency, executive functioning and processing speed and monitoring, as well as the Coping Inventory of Stressful Situations, providing scores on task-, emotion- and avoidance-focussed coping styles, and the Perceived Stress Scale. Linear regressions were used to determine the relative contribution of neuropsychological functioning and coping style to perceived stress. Results: Higher premorbid IQ and working memory were associated with higher stress levels. Predominant emotion-focussed strategies and low use of task-focussed coping were associated with higher stress. Discussion: The results support a role for neuropsychological functioning and coping style in predicting levels of perceived stress in FEP. Better overall cognitive functioning was related to more stress. This suggests that lower intellectual functioning may provide some protection to the experience of stress around the time of a first psychotic episode. Potential mechanisms for this finding are discussed.

**148 MS HUI-MINN CHAN**

**IS CHRONIC SCHIZOPHRENIA A FRONTOTEMPORAL DEMENTIA? A NEUROCOGNITIVE PERSPECTIVE**

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Background: Schizophrenia and frontotemporal dementia (FTD) have historically been considered two very different disorders. Recent research, however, has shown that there are important similarities between chronic schizophrenia and FTD in terms of clinical presentation, neurocognition, and neuropathology.

Objective: The main aim of this research is to compare and contrast neurocognition in chronic schizophrenia and FTD.

Methods: Retrospective neuropsychological data of 26 patients with chronic schizophrenia and 37 patients with FTD was obtained from a clinical database. Tests were categorised into 16 cognitive domains and an average z-score derived for each of the domains. Statistical analyses included “traditional” difference of means analyses as well as analyses of equivalence between the groups, using overlap percentages (OL%) of the distribution of z-scores within each domain.

Results: An independent samples t-test revealed the two groups to be significantly different statistically only in the domain of Switching. A means graph showed largely similar cognitive profiles across most domains. OL% was high between the groups for all of the domains. Similarly, a graph with individual means and 95% confidence intervals of the mean of the two groups revealed a large degree of overlap.

Conclusions: The current analyses of retrospective neuropsychological data revealed that patients with chronic schizophrenia and FTD performed almost identically across most cognitive domains with significant differences in only one domain. This finding contributes to a growing body of literature showing that chronic schizophrenia and FTD may not be as dissimilar as previously suggested and that in some patients may be two sides of the same coin.

**149 MR ORWA DANDASH**

**ALTERED STRIATAL FUNCTIONAL CONNECTIVITY IN SUBJECTS WITH AN AT-RISK MENTAL STATE FOR PSYCHOSIS**

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Recent functional imaging work in individuals experiencing an at-risk mental state (ARMS) for psychosis has implicated dorsal striatal abnormalities in the emergence of psychotic symptoms, contrasting with earlier findings implicating the ventral striatum. Our aims here were to characterize putative dorsal and ventral striatal circuit-level abnormalities in ARMS individuals using resting-state fMRI, and to investigate their relationship to positive psychotic symptoms. Resting state fMRI was acquired in 74 ARMS subjects and 35 matched healthy controls. An established method for mapping ventral and dorsal striatal functional connectivity was used to examine corticostriatal functional integrity.
Positive psychotic symptoms were assessed using the Comprehensive Assessment of At Risk Mental State (CAARMS) and the Positive and Negative Syndrome Scale (PANSS). Compared to healthy controls, ARMS subjects showed reductions in functional connectivity between the dorsal caudate and right dorsolateral prefrontal cortex, left rostral medial prefrontal cortex and thalamus, as well as between the dorsal putamen and left thalamic and lenticular nuclei. ARMS subjects also showed increased functional connectivity between the ventral putamen and the insula, frontal operculum and superior temporal gyrus bilaterally. No differences in ventral striatal (i.e., nucleus accumbens) functional connectivity were found. Altered functional connectivity in corticostriatal circuits were significantly correlated with positive psychotic symptoms. Together, these results suggest that risk for psychosis is mediated by a complex interplay of alterations in both dorsal and ventral corticostriatal systems.

150  DR SHONA FRANCEY

SHOULD ANTIPSYCHOTIC MEDICATION ALWAYS BE GIVEN FOR FIRST-EPIEODE PSYCHOSIS?

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The substantial reductions in the duration of untreated psychosis that has resulted from the establishment of early psychosis services across the world calls for a re-evaluation of the interventions that are routinely offered. It is possible that the immediate introduction of antipsychotic medication may not be necessary for all first-episode psychosis cases, but that potentially safer interventions, which may be more acceptable to many patients, such as comprehensive psychosocial intervention, may constitute effective treatment at least for a subgroup of patients. These more benign treatments may be more effective very early in the course of the illness as proposed by the clinical staging model.

The STAGES Study is a randomized controlled trial currently underway at EPPIC in Melbourne designed to test outcomes for first-episode psychosis patients in response to two different treatments: intensive psychosocial intervention plus antipsychotic medication versus intensive psychosocial intervention plus placebo. This novel study will provide evidence as to whether intensive psychosocial intervention alone is sufficient for a subgroup of first-episode psychosis patients in a specialised early intervention service, and provide a test of the heuristic clinical staging model. By experimentally manipulating duration of untreated psychosis, the study will also test the effect of delaying the introduction of antipsychotic medication, and help to disentangle the effects of antipsychotic medications and the putative neurobiological processes associated with brain changes and symptom profiles in the early phase of psychotic disorders. Progress to date in this challenging study will be presented.

151  DR LITZA KIROPOULOS

THE EFFECTIVENESS OF A SPECIALIZED CBT-BASED INTERVENTION FOR THE TREATMENT OF DEPRESSION AND ANXIETY IN THOSE NEWLY DIAGNOSED WITH MS: A FEASIBILITY STUDY

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Background: To date, there is a lack of systematic research examining the effectiveness of Cognitive Behavioural Therapy (CBT)-based psychological interventions in those newly diagnosed with MS (i.e., within 5 years of receiving an MS diagnosis) specifically targeting treatment of depression and anxiety symptoms, adjustment to illness, management of fatigue and pain symptoms and sleep difficulties in the Australian and international contexts. This has been suggested to be a time point where potential improvements in mental health can be made in those with MS. Hence, as part of the current trial we have developed and trialled a specialized treatment package for the treatment of depression and anxiety and related psychosocial factors such as pain, fatigue and sleep difficulties in a depressed, newly diagnosed, MS population which has not been otherwise undertaken in the Australian and international contexts.

Methods: So far 12 participants have been recruited into the trial and recruitment of research participants is still being undertaken. Participants are randomly assigned to an 8-week CBT based intervention or a treatment as usual control condition. Those allocated to the intervention arm undertake the 8 week individual face-to-face CBT intervention with a clinical psychologist at the Royal Melbourne Hospital City Campus. Eligibility criteria includes: a) confirmed diagnosis of relapsing-remitting or secondary progressive disease course of MS confirmed by a neurologist; b) a score of 10 or more on the BDI-2; c) willingness to abstain from psychological treatment for depression and anxiety during the trial (which is 20 weeks in total); and d) a clinical diagnosis for Major Depressive Disorder using the Structured Clinical Interview for DSM Disorders (SCID) (First et al., 1995). All participants taking part in the study complete pre, post and 3 month follow up assessment questionnaires. Level of depressive symptoms are measured with the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) and level of anxiety symptoms are measured using the Spielberger State-Trait Anxiety inventory (STAI) (Spielberger et al., 1983).
Results and Conclusions: Preliminary examination of trends in the data indicate that those in the specialised CBT intervention arm have shown improvements in their depressive and anxiety symptomatology.

152 MR BERND MERKEL

COMPARISON OF HIPPOCAMPAL VOLUMES AS AN EARLY BIOMARKER FOR ALZHEIMER’S DISEASE

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With increasing longevity worldwide, the prevalence of age-related diseases such as dementia, in particular Alzheimer’s Disease (AD), is also increasing. AD is the most common type of dementia, but to date there is no effective treatment. An impediment to therapeutic approaches is the lack of firmly established biomarkers of AD. Potential biomarkers include total tau protein (t-tau) and Aβ42 in cerebrospinal fluid as well as neuroimaging (MRI, PET). The hippocampus (HC) is a brain structure that is selectively vulnerable to pathology in AD with volume loss. Quantitative measures of HC volume loss on MRI have been shown as a strong predictor of AD diagnosis and progression. However, accurate determination of HC volume changes still remains a challenge. In this work, we analyse hippocampal volumes from 10 older adults with subjective memory complaints (SMC) or mild cognitive impairment (MCI), who are at increased risk of developing AD in the future. We compared HC volumes calculated by automated software methods (FreeSurfer, FSL) with manually drawn ROI volumes, being the gold standard for evaluating HC atrophy, and with an in-house developed template based on healthy older subjects for registration.

To compare the different methods, we calculated Pearson correlations and analysed both single left and right HC volumes as well as the total HC volume. FreeSurfer results were generally larger than FSL results, which themselves are larger than our own template and manually drawn ROIs. Without correcting the volumes for IntraCranialVolume (ICV), only the correlations between the manually drawn ROIs in the left and right HC and our ANTS template based measurements were significant at the level of r ≥ 0.686 (p<0.05). We also performed Pearson correlations across the 4 groups after correcting for ICV. There was a significant correlation in volumes between the ANTS template vs manually drawn ROIs (0.765, p=0.010, left HC and 0.665, p=0.036, right HC) as well as between Freesurfer vs manual volumetry (0.691, p=0.027, left HC and 0.775, p=0.008, right HC). FSL performed worse in both left and right HC with no correlation at all. Templates for MRI registration, which are based on older adults, may be more accurate in determining HC volume calculation. They are particularly useful if manual segmentations as the gold standard are not feasible or available and may be a quicker alternative to packages like FreeSurfer. However, performing the non-linear registrations may still require significant computing resources in order to achieve results in a reasonable time-frame.

153 DR TAMMIE MONEY

SIGNIFICANT INCREASE IN SELENIUM BINDING PROTEIN 1 EXPRESSION IN SUBJECTS WITH SCHIZOPHRENIA BY MICROARRAY PROBE SET: IMPLICATIONS FOR ISOFORMS

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We previously reported a significant upregulation of selenium binding protein 1 (SELENBP1) in the cortex of three separate cohorts of subjects with schizophrenia. However, the consequence of this upregulation in the brain is unclear. The aim of this study was to analyse recent microarray data from a well characterised cohort of subjects with schizophrenia who have a significant downregulation of the muscarinic M1 receptor (CHRM1), in order to identify the changes in expression of SELENBP1. In addition, to identify whether it is related to changes in specific regions of the exon.

Methods: Postmortem brain tissue from Brodmann’s area (BA9) was obtained from the Victorian Brain Bank Network from 15 controls and 30 subjects with schizophrenia, (15 subjects with low levels of CHRM1 binding and 15 subjects with normal levels of CHRM1 binding as described previously). An Affymetrix microarray compared mRNA expression between controls and the two groups of subjects with schizophrenia. There were 16 probe sets used in the microarray for SELENBP1, with each probe set consisting of two or three probes. The expression of SELENBP1 was analysed between subjects with schizophrenia and controls using two way ANOVA by probe set and by individual probes with Bonferroni post test.

Results: There was a significant effect of diagnosis (F= 49.112,672 p<0.0001) and probe set (F= 99.4815, 672 p<0.0001) on the expression of SELENBP1, but there was no significant interaction (F= 1.10430, 672 p = 0.3226). A Bonferroni post test revealed that compared to controls, there were five probe sets that were significantly different in the
subjects with schizophrenia with low CHRM1 binding (p<0.05). However, only one probe set was significantly different to control in the subjects with schizophrenia with normal CHRM1 binding (p<0.05).
In contrast, there were four individual probes that were significantly different to controls in the subjects with schizophrenia with low CHRM1 binding (p<0.05). In the group of subjects with schizophrenia with normal levels of CHRM1 binding, there were three probes that were significantly different compared to control (p<0.05). Of the probes that were significantly different in the groups of subjects with schizophrenia, only one probe was different in both groups.
Conclusions: These results suggest that the probes that are differentially expressed between controls and subjects with schizophrenia may represent different isoforms of SELENBP1. If confirmed, these isoforms could affect the functionality of the SELENBP1 protein and could begin to uncover a role for SELENBP1 upregulation in schizophrenia.

154 DR BARNABY NELSON

TRAUMA AND RISK OF DEVELOPING PSYCHOSIS IN A HIGH CLINICAL RISK POPULATION: RESULTS FROM A MEDIUM TO LONG-TERM FOLLOW-UP STUDY

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Studies indicate a high prevalence of childhood trauma in patient cohorts with established psychotic disorder and in those at risk of developing psychosis. A causal link between childhood trauma and development of psychosis has been proposed. We aimed to examine the association between experience of childhood trauma and the development of a psychotic disorder in a large “Ultra High Risk” (UHR) for psychosis cohort. The data were collected as part of a longitudinal cohort study of all UHR patients recruited to research studies at the Personal Assessment and Clinical Evaluation clinic between 1993 and 2006. Baseline data were collected at recruitment to these studies. The participants completed a comprehensive follow-up assessment battery (mean time to follow-up 7.5 years, range 2.4–14.9 years), which included the Childhood Trauma Questionnaire (CTQ), a self-report questionnaire that assesses experience of childhood trauma. The outcome of interest was transition to a psychotic disorder during the follow-up period. Data were available on 233 individuals. Total CTQ trauma score was not associated with transition to psychosis. Of the individual trauma types, only sexual abuse was associated with transition to psychosis (P = .02). The association remained when adjusting for potential confounding factors. Those with high sexual abuse scores were estimated to have a transition risk 2–4 times that of those with low scores. The findings suggest that sexual trauma may be an important contributing factor in development of psychosis for some individuals.

155 MS ANASTASIA POURLIAKAS

EXPLORING VULNERABILITIES TO FEAR OF PAIN IN CHRONIC PAIN: THE ROLE OF ANXIETY SENSITIVITY AND DISTRESS TOLERANCE

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Background: Approximately 17 to 20 percent of the Australian population go on to develop chronic pain (Blyth et al., 2001). The experience of pain has been conceptualised as consisting of cognitive, affective and behavioural components. The Fear Avoidance Model (FAM) proposes that if an individual (mis)interprets their acute pain in a catastrophic manner, these interpretations can give rise to pain-related fear. This may then lead to safety seeking behaviours, the long term consequences of which can often lead to disability, disuse and lowering of the pain threshold, leading to an experience of chronic pain (Asmundson, Norton, & Vlaeyen, 2004). The current study examined the FAM model of chronic pain in a clinical sample by examining the relationships between Anxiety Sensitivity (AS), Distress Tolerance (DT) and fear of pain. Anxiety sensitivity (AS) is the fear of anxiety related bodily sensations, which arise from the belief that these sensations have harmful somatic, psychological or social consequences (Asmundson & Taylor, 1996). Distress tolerance (DT) relates to the perceived capacity to withstand negative emotional and/or other aversive states (e.g., physical discomfort) (Leyro, Zvolensky, & Bernstein, 2010). It was hypothesised that the higher in AS and lower in DT will show higher levels of pain catastrophising which will lead to greater fear of pain and that those high in AS and low in DT will show greater fear of pain than individuals showing higher levels of vulnerability on only one of these factors.

Method: A total of 51 participants with an average age of 52 years (range: 23 to 85 years) and an average length of pain experienced of 10.4 years (range:3 months to 40 years) have been recruited into the current study so far. Participants have been recruited from the Pain Clinic at the Royal Park Campus of the Royal Melbourne Hospital. Potential participants were approached by the student researcher and asked to complete a questionnaire pack either while they waited to see their pain specialist in the Pain Clinic or had the option to complete the questionnaire pack at a time and place of their choice and return to the researchers with a reply paid envelope. Participants completed the
Anxiety Sensitivity Index – 3, the Distress Tolerance Scale, the Depression, Anxiety and Stress Scale, the West Haven-Yale Multidimensional Pain Inventory, the Pain Anxiety Symptoms Scale – 20 and the Pain Catastrophising Scale. Results and Conclusions:The current study is still recruiting participants. Trends in the data will be discussed.

156 DR VAIDY SWAMINATHAN

ALTERED EPIDERMAL GROWTH FACTOR RECEPTOR LEVELS IN DORSOLATERAL PREFRONTAL CORTEX MAY BE IMPLICATED IN SUICIDALITY IN SCHIZOPHRENA

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Background: Emerging evidence demonstrates dysregulation of the Epidermal Growth Factor (EGF) system in schizophrenia (SCZ) with increased levels of the EGF receptor (EGFR) and decreased levels of EGF in both brain and blood. We have shown clozapine transactivates EGFR to augment signalling and this may be related to its clinical effects. We examined EGFR in post-mortem human brain tissue from people with SCZ and healthy controls.

Methods: EGFR messenger RNA (mRNA) expression was measured by in-situ hybridization (ISH) and qRT-PCR and protein levels by Western blotting in dorsolateral prefrontal cortex (DLPFC) (BA46) from 37 persons with SCZ and 37 healthy controls.

Results: EGFR protein was significantly (p<0.04) increased in SCZ (1.63±1.15, mean±SD) compared to controls (1.218±0.21). There was no difference in mRNA expression between patients and controls using ISH or qRT-PCR. Protein levels were highly significantly correlated with mRNA levels in SCZ (r=0.57, p=0.0002) and healthy controls (r=0.71, p=0.0001). In SCZ, those who had no history of suicidality had significantly higher levels of EGFR protein (0.24±0.07) and mRNA (0.872±0.03) compared to those with suicidality (-0.13±0.10/0.73±0.06).

Conclusions: EGFR protein but not mRNA levels are increased in the DLPFC in SCZ indicating a post-transcriptional dysregulation of effect. The pronounced effect of EGFR levels in suicidality and our data implicating clozapine augmentation of EGFR signalling suggests this may be a relevant mechanism in mediating the drug’s anti-suicidal properties.

157 DR SINNATAMBY SUJEEVAN

SERUM EPIDERMAL GROWTH FACTOR LEVELS ARE REDUCED IN PEOPLE WITH TREATMENT RESISTANT SCHIZOPHRENIA AND MODULATED BY CLOZAPINE TREATMENT

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Background: Up to 45% of patients with schizophrenia are treatment resistant to conventional drugs leaving clozapine as the only effective option. Its severe side-effects however limit it to a late stage option and the development of a biomarker to predict treatment response would be of high clinical utility. Our previous data demonstrate clozapine augments epidermal growth factor receptor (EGFR) signalling and hence we examined if EGF levels may be altered in treatment resistant schizophrenia (TRS) and are influenced by clozapine treatment.

Study objectives: To determine if EGF levels are influenced by clozapine in TRS and can serve as a biomarker for clozapine response

Methodology: Serum EGF levels were measured by ELISA in patients with TRS at baseline, 2, 6 and 26 weeks of clozapine treatment and in age and sexed matched healthy controls. Positive and Negative Syndrome Scale (PANSS) and CGI data were collected at baseline, 6 and 26 weeks.

Results: In the patient group, the mean reduction in total PANSS score was 20.4 and CGI was 1.82 (n=56). Twenty-six (46%) patients responded (≥20% reduction in PANSS score). Mean EGF levels at base line were 272pg/ml (±223, SD), at 2weeks 242pg/ml (±190), at 6 weeks 400pg/ml (±228) and at 26 weeks 409pg/ml (±275). These values were significantly (p<0.01) lower than that of the controls (mean 749pg/ml ±328). Mean EGF levels increased over the 26 weeks in patients by 169% (±269) and this became significant by 6 (P=0.013) and 26 weeks (P=0.019). There were no significant main correlations between EGF levels and clinical response.

Conclusions: EGF levels were significantly decreased in people with TRS and were significantly increased with clozapine treatment indicating that clozapine is able to modulate the EGF system in patients. There was however no relationship with symptom change suggesting it is unlikely to be a suitable biomarker for clozapine response.
ON THE ORIGINS OF RENAL CELL CARCINOMA, VESICOURETERIC REFLUX AND C (OPITZ TRIGONOCEPHALY) SYNDROME: A COMPLEX PUZZLE REVEALED BY WHOLE GENOME DNA SEQUENCING OF AN INHERITED T(2;3) TRANSLOCATION

JOHN M. DARLOW, LYNNE MCKAY, MARK G. DOBSON, STEPHANIA SCALA, DAVID E. BARTON, AND INGRID WINSHIP

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