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Association between borderline anaemia and outcome in women undergoing abdominal surgery


Introduction

Anaemia has been recognised as a risk factor for poor post-operative outcome across a variety of surgical specialties. However, most evidence defines anaemia using the World Health Organization (WHO) definition, which is sex-based and unchanged since the 1950’s. The data used by the WHO to determine haemoglobin concentration [Hb] relatively underrepresents women and data on iron status was not fully available. We hypothesised that women relative to women with a [Hb] ≥ 130 g/L, women with a [Hb] of 120 – 129 g/L would have worse post-operative outcomes.

Methods

We conducted a retrospective cohort study of all women who underwent elective major abdominal surgery at Austin Health between July 2013 and July 2018. Patients were stratified as anaemic, borderline anaemic and not anaemic according to pre-operative [Hb]. We collected data on baseline characteristics, preoperative laboratory results, and postoperative outcomes. Univariate statistical analysis between borderline anaemic and not anaemic groups was performed. Multivariate matched analysis corrected for procedure and comorbidities was also completed.

Results

Relative to the non-anaemic group, borderline anaemic women demonstrated a higher risk of complication (55 [16%] vs. 110 [11.4%]; p = 0.026), increased length of hospital stay (3.0 [1.1 – 6.2] days vs. 2.2 [1.0 – 5.0] days; p = 0.017) and reduced DAOH at day 30 (24.6 [8.5] vs. 25.6 [5.8]; p = 0.017) and day 90 (83.2 [11.0] vs. 84.1 [10.9]; p = 0.03). Following multivariate analysis, the previously demonstrated differences in outcomes reduced in magnitude, and statistical significance was lost. However, the difference in point prevalence for some of these metrics between the groups, particularly complication, means that type II error cannot be excluded.

Conclusion

In women undergoing major elective abdominal surgery, borderline anaemia may be associated with poorer outcomes than non-anaemia. However, concomitant comorbidity and procedure type are significant confounding factors. We conclude that the current recommendation that a [Hb] of 120 – 129 g/L is “adequate” for women presenting for abdominal surgery is not fit for purpose and in need of revision. There is a clear need for further studies better defining the relationship between procedure, comorbidities, sex and pre-operative [Hb].

References

Financial burden of postoperative complications following colonic resection: a systematic review

Aim
Colonic resection is a common surgical procedure associated with a high rate of post-operative complications. The development of complications is expected to be a major contributor to hospital costs. This systematic review aims to outline the health costs of postoperative complications following colon resection surgery and to determine the association between complication severity, length of stay, 30-day readmission and mortality, and costs.

Methods
We searched the literature using the MEDLINE, EMBASE, Cochrane and EconLit databases from January 2010 to February 2019 to identify English studies containing an economic evaluation of postoperative complications following colonic resection in adult patients. Colon resection was defined as complete excision of any part of the large bowel (excluding rectum). Eligible study design included randomised and non-randomised controlled trials, comparative observational studies and conference abstracts. Risk of bias was assessed using validated assessment tools. Findings are reported as a narrative synthesis.

Results
Thirty-four articles met the eligibility criteria. Our findings demonstrate a substantial degree of heterogeneity in study design, methodology used to calculate cost and defining and reporting on complications. We found a high overall complication incidence with associated increased costs and resource utilisation following colonic resection surgery. Increasing complication severity and complication count were associated with increased resource use. Hospital readmissions are highlighted as a significant financial burden and postoperative complications are associated with greater incidence of hospital readmissions. Postoperative complications were found to result in increased hospital length of stay and mortality incidence. Limitations include few high-quality costing studies and substantial study heterogeneity preventing quantitative analysis of cost results.

Conclusion
Postoperative complications in colonic resection surgery appear to be associated with a significant financial burden. High quality, consistent, prospective economic studies are still needed to accurately evaluate the cost of complications arising from colonic resection surgery.
The hospital costs associated with postoperative complications following colon resection surgery: a cohort study

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5. Department of Surgery, Austin Health, Heidelberg, VIC 3084, Australia.

Aim
Colonic resection is a common surgical procedure associated with a high rate of post-operative complications. Our aim is to estimate the in-hospital costs of complications and to identify perioperative variables associated with complication development following colon resection surgery.

Methods
487 patients from 2013 to 2018 were included. Postoperative complications were defined as any deviation from the normal postoperative course and graded according to the Clavien-Dindo classification system. In-hospital cost of index admission, excluding preoperative costs, is reported in 2019 United States Dollars. Regression modelling was used to investigate the relationship of a priori selected perioperative variables and presence of complications.

Results
The overall complication prevalence was 69.6% (95%CI: 65.5% to 73.7%). Presence of complications was significantly associated with Charlson Comorbidity Index (Odds ratio per 1-point increase: 1.09; 95%CI:1.02 to 1.17), preoperative albumin levels (Odds ratio per 1-point increase: 0.94; 95%CI: 0.90 to 0.98) and open as compared to laparoscopic resection (Odds ratio: 2.41; 95%CI: 1.32 to 4.42). Median [interquartile range] cost of patients with postoperative complications was significantly increased as compared to patients without complications ($17,963 [13,533:25,178] vs $12,578 [10,196:16,140]; p<0.0001). Increasing complication count was associated with a significant increase in hospital costs (p≤0.013). Costs were significantly increased for all complication severity grades (p<0.0001) except for grade V complications that did not reach statistical significance (p=0.090). Patients with complications had an increased median hospital length of stay (8 [6:13] vs 5 [4:6] days; p<0.0001). No significant difference was identified in 30-day readmission rates between complicated (12.7%) and uncomplicated patients (11.5%); p=0.766.

Conclusion
Our study highlights postoperative complications as a key target for cost containment strategies. We demonstrate a high incidence of postoperative complications following colon resection associated with an increase in hospital costs and hospital length of stay.
Inducible left ventricular outflow tract obstruction is associated with a higher incidence of perioperative cardiac arrest in liver transplantation

**Background:** Inducible left ventricular outflow tract obstruction (LVOTO) is often encountered in liver transplant (LT) candidates during cardiac workup. While the impact of LVOTO on adverse cardiovascular haemodynamics is well reported, it is unclear whether it predisposes to perioperative cardiovascular complications post LT.

**Methods:** Consecutive patients undergoing dobutamine stress echocardiography were evaluated from a LT centre between 2010-2017. Inducible LVOTO was defined as LVOT gradient ≥36mmHg. Perioperative major adverse cardiovascular events (MACE) at 30 days and all-cause death were recorded from a prospectively maintained LT database and supplemented by electronic medical record review.

**Results:** We evaluated 560 patients who underwent DSE during LT workup, 319 of which progressed to transplant. Inducible LVOTO was observed in 68 patients (21.3%). A higher baseline cardiac output (7.7 vs. 7.0 L/min, p=0.002) predicted for development of inducible LVOTO. Seventy-seven patients (4.1%) experienced a MACE including five deaths, 19 cases of heart failure, 11 cardiac arrests, 10 acute coronary syndromes and 46 arrhythmias (VT/AF). Overall MACE occurred in 17/68 patients (25.0%) with LVOTO and 60/251 (23.9%) without (p=0.85). However, there was a significantly increased risk of resuscitated peri-operative cardiac arrest in patients with LVOTO (7.4% vs. 2.4%, p=0.04). Patients with LVOTO also required significantly greater volumes of fluid intraoperatively (8.37L vs. 6.71L, p=0.043).

**Conclusions:** Inducible LVOTO is a frequent finding occurring in 21.3% of LT candidates. Despite higher intraoperative fluid resuscitation, LVOTO increased the risk of perioperative cardiac arrest. Patients with LVOTO undergoing liver transplantation may benefit from heightened perioperative surveillance.
Existing models to assess perioperative cardiac risk demonstrate poor predictive validity in patients undergoing liver transplantation

**Background:** Liver transplantation (LT) is associated with risk for perioperative cardiovascular events. Although guideline recommended risk scores are well validated in non-cardiac surgery, there is uncertainty regarding their utility in LT.

**Methods:** Consecutive adult patients undergoing LT at the Victorian Liver Transplantation Unit between 2010 and 2017 were evaluated. Perioperative 30-day major adverse cardiovascular events (MACE) and all-cause death were recorded from a prospectively maintained transplantation database and supplemented by electronic medical record review. Perioperative risk for each patient was calculated using the Revised Cardiac Risk Index (RCRI), Charlson Comorbidity Index (CCI) and American Society of Anaesthesiologists Score (ASA) and subsequently assessed for predictive validity.

**Results:** Among the 704 adult patients that underwent workup for LT, 462 proceeded to transplantation (mean age 52±13, 67.5% male). A total of 51 (11%) patients had perioperative MACE within the 30-day post-operative period. Events included 26 episodes of cardiac failure, 15 resuscitated cardiac arrests, 16 acute coronary syndromes and 10 episodes of ventricular tachycardia. Predictive capability of the assessed scores is reported in Table 1. The risk predictive ability of the RCRI, CCI and ASA scores were low, with all reporting an area under the curve (AUC) <0.60. A high risk score, as defined by guideline recommendations, demonstrated a modest negative predictive value (NPV) and a low positive predictive value (PPV).

**Conclusion:** Current preoperative risk prediction algorithms have poor predictive ability for cardiac events in a contemporary cohort of LT patients. Better risk prediction algorithms in this group of patients are warranted.

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<td>RCRI ≥3</td>
<td>91%</td>
<td>21%</td>
<td>0.57</td>
<td>0.51-0.64</td>
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<tr>
<td>CCI ≥5</td>
<td>92%</td>
<td>13%</td>
<td>0.56</td>
<td>0.49-0.63</td>
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<tr>
<td>ASA ≥4</td>
<td>88%</td>
<td>10%</td>
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Beta blocker use increases the risk of perioperative cardiac events in liver transplant patients

**Background:** Recent evidence has linked beta blocker (BB) use with perioperative major adverse cardiovascular events (MACE) after non-cardiac surgery. BB are often used for treatment of portal hypertension in liver disease. We sought to determine whether BB use was associated with adverse perioperative outcomes in liver transplantation (LT).

**Methods:** Consecutive adult patients undergoing LT between 2010 and 2017 in the Victorian Liver Transplantation Unit were evaluated. Beta-blocker use, perioperative 30-day MACE (acute coronary syndrome, cardiac arrest, cardiac failure and ventricular tachycardia), and all-cause mortality were recorded from a prospectively maintained database.

**Results:** We evaluated 704 patients who underwent workup for LT. Of these, 462 proceeded to transplant (mean age 52±13; 67.5% male). There were 84 (19.8%) patients on BB at the time of surgery. Patients on BB were older (55±10 vs 52±13 years; p=0.025), and more frequently had coronary disease (15.5% vs 6.2%; p=0.005) and atrial fibrillation (22.6% vs 2.6%; p<0.001). There were 51 (11%) MACE and five deaths. BB use was associated with higher MACE (16.7% vs 8.5%; p=0.026), but not all-cause mortality (2.4% vs 0.9%; p=0.25). Multivariable logistic regression was used to adjust for age, Revised Cardiac Risk Index, coronary disease, atrial fibrillation and post-operative bleeding or infection. BB use was independently associated with increased risk of perioperative MACE (OR 2.06, 95%CI 1.14-3.71; p=0.017).

**Conclusions:** BB use in patients undergoing LT was independently associated with higher perioperative MACE. This study adds to a growing body of evidence suggesting an association of BB use with adverse perioperative cardiac events.
Hepatorenal syndrome in patients undergoing liver transplantation is an independent risk factor for perioperative cardiac complications

**Background:** Hepatorenal syndrome (HRS) is a serious complication of cirrhosis associated with a poor survival in the absence of liver transplantation (LT). Although HRS confers higher risk of complications due to cirrhosis, it is unclear whether it leads to increased risk of perioperative major adverse cardiovascular events (MACE) following LT.

**Methods:** Consecutive patients that underwent pre-liver transplant (LT) workup between 2010-2017 were included. All patients underwent a dobutamine stress echocardiogram (DSE) as part of the work-up. HRS was diagnosed using guideline-based criteria. MACE was recorded from a prospectively maintained transplantation database and supplemented by electronic medical record review.

**Results:** A total of 560 patients (mean age 56±12 years, 75% male) underwent workup for LT. Among these 319 proceeded to LT with viral hepatitis (37%) being the primary etiology. Seventy-six (23.8%) MACE events occurred in the 30-day perioperative period. This included 5 deaths, 19 cases of heart failure, 11 cardiac arrests, 9 acute coronary syndromes and 46 arrhythmias (VT/AF). A significantly higher proportion of patients with HRS developed MACE (32/85, 37.7%) compared to those without HRS (44/234, 18.8%) (p<0.001). On multivariable logistical regression, after adjusting for age, gender, diabetes, pre-existing history of AF, NASH, BMI and an abnormal DSE, HRS was strongest predictor of perioperative MACE (OR 2.67, 95%CI 1.27-4.68, p=0.008).

**Conclusions:** HRS is associated with a higher risk of perioperative MACE when undergoing liver transplantation. This association is maintained after adjustment for comorbid conditions. Incorporating HRS in cardiac risk prediction algorithms may further improve risk stratification of patients undergoing LT.
Background

The total number of Atrial Fibrillation (AF) hospitalisations in Australia continues to increase more than for any other cardiovascular condition(1)

- In Victoria there are ~15,000 Emergency Department (ED) presentations a year
- The lifetime risk of ischaemic stroke among patients >65 years is high(2)
- Australian research has suggested that program-management of AF improves mortality and other adverse outcomes(3)
- Preliminary work at the Austin in 2016-2017 indicated significant opportunities to reduce practice variation, and to close treatment gaps that have been observed globally(4)

Aims

- To review patients as soon as possible after presenting to ED with AF
- To ensure provision of a basic suite of investigations (AF Care Set)
- To adhere to the basic guideline prescribing program
- To promote early follow up with family doctors and appropriate clinics (i.e. cardiology, arrhythmia, heart failure and general medicine)

“Our rapid access clinic AF-Express (AF-X), was established to provide early review with emphasis on appropriate initial investigation, prompt clinical assessment and access to comprehensive treatment, with particular focus on stroke prevention. We work with patients and their families to deliver:

- Evidence-based care
- Individual, patient focused management
- Education and re-assurance for patients & their families”

Method

- AF-X uses hospital data systems to automatically identify patients who have presented to ED with AF
- Nurse-led clinic aimed at offering early review - within 5 working days
- We aim to review all ED presentations
- The AF Care Set is guaranteed: electrocardiogram, chest X-ray, serum creatinine & electrolytes, full blood count, echocardiography to assess structural heart disease & cardiac dysfunction
- After clinical assessment, patients are referred to the most appropriate follow-up
- Data (including a health questionnaire & experience measure) forms a clinical archive to facilitate clinician feedback & quality improvement activities

Results

In the first eight months of operation a total of 283 patient reviews occurred in AF-X:

- 178/551 ED presentations referred to AF-X
- 37 encounters referred by GP
- 27 encounters from ward services
- 46 patients were seen in clinic more than once

Data shows an increase in AF-X encounters, and significant downward trend in the number of ED encounters (Figure 2), explaining a preliminary finding of ~16% downward trend of all AF encounters. Supporting this evidence is the small number who re-present (1.8%) after being seen in AF-X as opposed to 9.3% who represent who have not previously been seen in AF-X (Figure 1)

Conclusion

1. AF-X is a health service improvement initiative that delivers an innovative multi-disciplinary service underpinned by health informatics
2. Quality, Safety, Efficiency and Access are directly or indirectly addressed in the management of patients with AF presenting to the ED
3. Preliminary findings suggest that early nurse-led review in the AF-X clinic may help reduce ED re-admissions, by ensuring consistent delivery of care
4. AF-X has the potential to serve as a template for development of other informatics-based scalable, nurse-led healthcare delivery programs

References

5. EQ-5D-5L Health Questionnaire Australia (English) © 2009 EuroQol Group EQ-SD 1™
Trends in traumatic spinal cord injury in Victoria, Australia: 2007 to 2015

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Background: Spinal cord injury (SCI) can have devastating and lasting effects on individuals and these injuries are associated with significant societal and economic burden. There is a need to understand the epidemiological patterns of traumatic SCI to inform the development of injury prevention strategies and the provision of health care and disability services.

Aims: This study aimed to examine trends in the incidence and causes of hospitalisations for traumatic SCI over a 9-year period.

Methods: We performed a retrospective review of major trauma patients who sustained a traumatic SCI using data from the population-based Victorian State Trauma Registry from 2007 to 2015. SCI was defined as an AIS (2005 version 2008 update) score ≥ 4 in the cervical, thoracic or lumbar spine, with the exclusion of cauda equina and nerve root injuries.

Results: There were 628 cases of traumatic SCI in Victoria over the 9-year study period. Most patients were men and the median age was 50 years (interquartile range: 30-68). Forty percent resulted from transport-related events and 26% from low falls. Fifty cases of SCI (8%) resulted from being struck by or a collision with an object. Of these, 17 (34%) resulted from diving into shallow water and 10 (20%) resulted from water sport activities.

The incidence of SCI did not change over the study period (IRR = 1.01, 95% CI: 0.98, 1.05; P=0.352). Similarly, there was no change in the incidence of SCI in motor vehicle occupants (IRR = 0.97, 95%CI: 0.91, 1.04; P=0.416), motorcyclists (IRR = 0.95, 95% CI: 0.87, 1.05; P=0.302), cyclists (IRR = 1.06, 95% CI: 0.95, 1.19; P=0.269) or pedestrians (IRR = 0.96, 95% CI: 0.75, 1.20; P=0.702). While the incidence of SCI resulting from high falls did not change over the study period (IRR = 1.01, 95% CI: 0.94, 1.09; P=0.706), the incidence resulting from low falls increased 8% per year (IRR = 1.08, 95% CI: 1.02, 1.15; P=0.009). These low fall events were commonly observed in those aged 65 years and older (61%), were incomplete cord injuries in the cervical spine (64%) and were isolated SCI injuries (96%).

Discussion and conclusions: Over a 9-year period, we observed no change in the overall incidence of traumatic SCI and an increase in the incidence of traumatic SCI resulting from low falls. Given the devastating effects on individuals and their families, continued efforts in primary prevention are required to reduce the burden of traumatic SCI.
A human sensory pathway connecting the foot to ipsilateral face that partially bypasses the spinal cord

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Abstract
Human sensory transmission from limbs to brain crosses and ascends through the spinal cord. Yet, descriptions exist of ipsilateral sensory transmission as well as transmission after spinal cord transection. To elucidate a novel ipsilateral cutaneous pathway, we measured facial perfusion following painfully-cold water foot immersion in 10 complete spinal cord-injured patients, 10 healthy humans before and after lower thigh capsaicin C-fiber cutaneous conduction blockade and 10 warm-immersed healthy participants. As in healthy volunteers, ipsilateral facial perfusion in spinal cord injured patients increased significantly. Capsaicin resulted in contralateral increase in perfusion, but only following cold immersion and not in 2 spinal cord-injured patients who underwent capsaicin administration. Supported by skin biopsy results from a healthy participant, we speculate that the pathway involves peripheral C-fiber cross-talk, partially bypassing the cord. This might also explain referred itch and jogger’s migraine and may be amenable to training spinal-injured patients to recognize lower limb sensory stimuli
EEG-fMRI with causal modelling can identify the driving node in focal epilepsy networks

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Aim
A clinical dilemma in epilepsy localization occurs when the epileptic discharges on EEG are spatially discordant from a brain lesion on MRI. We investigated the network relationship between these two regions, using simultaneous EEG-fMRI data and stochastic dynamic causal modelling1 (sDCM).

Methods
Three patients were identified meeting the following criteria: a solitary focal epileptogenic lesion, discordant scalp EEG localization, and an EEG-fMRI study showing significant peri-lesional activation. Simultaneous EEG and functional MRI data were acquired for one hour (3T MRI, echo-planar imaging, TR 3.0/3.2s, TE 30/40ms, voxels 3.0/3.4mm isotropic). The blood oxygen-level dependent time course was extracted from the two relevant regions. A set of plausible two-node bilinear sDCM models were evaluated for each patient, with the best-fit model in each case identified using Bayesian model selection and fixed-effects analysis.

Results
The same network model was found to have the highest probability in each case. It showed reciprocal excitatory connections between the lesion and the epileptic discharge node (strength 0.08 to 0.36Hz, Pr>0.99) and self-inhibition at each node (strength -0.05 to -0.22Hz). Scalp epileptic discharges corresponded to a driving input at the lesion (strength 0.009 to 0.017Hz, Pr>0.99), and a modulating influence on connectivity from the lesion to the epileptic discharge node.

Conclusion
EEG-fMRI can help to reconcile discordant EEG and structural MRI findings by revealing a multi-lobar network of inter-ictal epileptic activity. Causal modelling demonstrated the structural lesion as the most plausible driver of epileptic network fluctuations in each case. Hypothesis-driven application of causal modelling may be a useful method for identifying the driving node in similar cases of focal epilepsy.

References
Aim
Developmental and epileptic encephalopathies (DEEs) are a group of severe, early onset epilepsies, characterised by refractory seizures, frequent epileptiform activity, developmental delay and/or regression. DEEs are highly genetically heterogeneous with over 100 genes implicated. However, around half of all patients remain unexplained after molecular testing. We sought to identify genetic causes of unsolved DEEs through whole exome sequencing.

Methods
214 patients with a DEE who were negative for a DEE genetic panel, underwent whole exome sequencing, including 168 proband-parent trios, 21 proband-parent duos, and 25 proband singletons. Ultra-rare, nonsynonymous variants that followed de novo dominant, compound heterozygous, newly homozygous or X-linked hemizygous pattern of inheritance were prioritised.

Results
We identified pathogenic or likely pathogenic variants in 36/214 (16.8%) of our unsolved DEE patients: 11/36 (31%) were biallelic, with homozygous or compound heterozygous inheritance. 13/36 (36%) of solved patients had variants in known DEE genes, which had been missed on screening due to insufficient coverage or undetected mosaicism. 12/36 (33%) had pathogenic variants in genes associated with neurodevelopmental disorders, but not well described in DEEs. We identified de novo variants in 4 extremely rare genes causing DEEs: CMPK2, CPSF1, IRF2BPL and KCNV2. In the remaining 178 patients, we identified de novo variants of uncertain significance in 110 genes not previously linked to DEE or other neurological disorders.

Conclusion
WES in 214 patients with unsolved DEEs identified a genetic cause for 16.8% patients, implicating novel candidate DEE genes, confirming the genetic heterogeneity of the DEEs and emphasising the need for large cohorts of patients to identify rare causes of DEEs. Recessive causes of DEE were found in a higher than expected number of patients for a cohort of apparently sporadic DEEs, highlighting the importance of considering this inheritance pattern, even in families without a history of consanguinity.
Aim
Natural history studies (NHS) and patient registries are informing diagnosis and management of the developmental and epileptic encephalopathies (DEEs). Understanding the natural progression and features of these rare diseases is required to position the community to determine the effectiveness of novel therapies, and to promptly identify suitable patients for Precision Medicine trials. The goals of NHS are to: 1) understand the disease course, delineating how a disease begins and evolves over time; 2) improve diagnosis of comorbidities, influencing patient care and inform healthcare management; 3) provide a baseline for Precision Medicine trials; and 4) assess response to therapies in comparison to natural disease progression.

Methods
Key stakeholders, including families, and clinicians will form an Australia-wide network focused on the DEEs. We will develop an online patient registry, with functionality to enable information to be provided by both parents, carers and patients, as well as clinicians. Information will be collected by questionnaire and data regarding investigations such as gene variants, electroencephalogram (EEG), neuroimaging and information from medical records will be entered.

Results
Paediatric epilepsy experts from each state will engage a network including all Australian paediatric neurologists. Key stakeholders and personnel have been identified. The Epilepsy Research Centre’s Epilepsy Genetics Database has 23,000 participants (~50% affected) and the DEE NHS will leverage our expertise in phenotypic delineation and our extensive track record of family engagement and clinical trial experience.

Conclusion
The DEE NHS will be the first Australia-wide epilepsy patient registry, with cohorts engaged and keen to participate in studies, including trials, and a network of committed clinicians and researchers. As Precision Medicine trials are developed, we will be ideally positioned to take trials forward with our network and understanding of the natural history of these debilitating diseases.
A Prospective Study of Patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Identifying Ultrasonographic Features for Diagnosis and Prognosis

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Background
There are no current biomarkers in CIDP, with diagnosis and treatment monitoring largely based on clinical parameters. High frequency ultrasound of peripheral nerves can reflect pathophysiological changes in CIDP, as well as changes with treatment, in a quick, non-invasive, and painless manner. This project aims to further the identification of useful diagnostic, prognostic and treatment-related biomarkers utilizing parameters found on neuromuscular ultrasound (NMUS).

Methods
We conducted a standardized clinical and ultrasonographic assessment of patients with CIDP at both Wake Forest Baptist Medical Center, NC (October to November 2017) and Austin Health, Melbourne, Australia (July 2018 to current). Our protocol focused on bilateral whole length assessment of the median and ulnar nerves, with unilateral assessment of radial, tibial, fibular and sural nerves. Correlation of clinical (disease duration, current clinical state, treatment history), electrodiagnostic (from most recent test) and ultrasound findings (in particular nerve size as measured by cross sectional area) was undertaken. 25 patients were studied at WFBMC neurodiagnostic laboratory, with data collection continuing at Austin Health (15 patients thus far).

Results
Of the 25 patients studied at WFBMC, all had abnormalities on ultrasound (as determined by focal nerve enlargement determined by increased cross sectional area), with 23 of 25 subjects having >=4 enlarged segments. All patients had at least one abnormality in either median or ulnar nerve, with no additional diagnostic information from other nerves tested. We analyzed our data in line with previously published diagnostic scores and protocols, and these findings will also be presented and discussed for typical vs atypical CIDP subtypes, as well correlation with clinical findings. Early data from the Australian cohort studied will also be presented.

Conclusions
This cross-sectional study of NMUS in patients with CIDP suggests assessment of bilateral median and ulnar nerves from wrist to axilla may be adequate in providing diagnostic information.
Abstract

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Co-Registration of Transcranial Doppler and Anatomical imaging (COTRADA)

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Background Transcranial Doppler (TCD) ultrasound has been extensively used in the diagnosis of intracranial arterial disease for more than 30 years. One of the primary limitations of the TCD technique has been the lack of any form of anatomical image information that is produced while scanning. This leads to TCD being particularly operator dependant, with the possibility for significant errors in vessel identification. We demonstrate the ongoing development of a technique that uses a radio frequency position location system as well as anatomical information from either CT or MR angiography, to provide guidance to a TCD operator while performing an ultrasound examination.

Methods A radio frequency position sensing system (Polhemus Fastrak, Polhemus, Vermont, USA) is combined with a TCD ultrasound system (Compumedics DWL, Melbourne, Australia) via the use of a synchronised pulse generator. The synchronised pulses allow the position of the TCD ultrasound probe in space to be correlated with both the ultrasound blood flow measurements, and the anatomical data stored in either a CT or MR angiographic image. A display system (InVesalius, Centro de Tecnologia da Informação Renato Archer, Brazil) is used to show the anatomical location being examined by the TCD ultrasound beam, in a manner similar to an image guided stereotactic surgery system.

Participants A group of five (5) participants will be recruited from acute stroke patients admitted to the stroke unit at Austin Health. Participants will receive an identical clinical TCD examination to that of the standard level of care, with the addition of the co-registration equipment being attached to the TCD ultrasound system.

Analysis Following TCD examination, the co-registered records of the ultrasound data and the CT or MR angiography data will be examined to determine the accuracy of operator identification of intracranial arteries. Additionally, the co-registered data will be used to optimise the functionality of the TCD co-registration system. The final end product of this research is intended to be a system suitable for point-of-care, image guided TCD ultrasound examination in the emergency department environment, with the goal of enhancing clinical decision making during the emergency treatment of stroke patients by providing accurate, continuous diagnosis of intracranial artery flow states.
The cerebral-placental-uterine ratio as a novel predictor of late fetal growth restriction: a prospective cohort study

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Aims
Despite being the biggest risk factor for stillbirth, the majority of cases of fetal growth restriction remain undetected antenatally. We aimed to evaluate which 36 week Doppler ultrasound parameters:
(i) best predict small-for-gestational-age (SGA; <10th, <5th & <3rd centile) infants
(ii) correlate most strongly with neonatal body composition measures reflecting fetal nutrient supply

Methods
347 nulliparas with singleton pregnancies prospectively underwent ultrasound examination at 36 weeks. The average pulsatility index (PI) of the placental umbilical artery (UA), fetal middle cerebral artery (MCA), ductus venosus, renal arteries, aortic isthmus, and maternal uterine arteries (UtA) were recorded. The cerebroplacental ratio (CPR) was calculated (UA PI/MCA PI). A new combination parameter, the CPR/Ua PI (cerebral-placental-uterine ratio, CPUR) was created. Infant customised birthweight centile, Ponderal Index and neonatal body fat percentage (BF%; measured with air displacement plethysmography) were recorded.

Logistic regression ascertained which parameters share a significant relationship with birthweight <10th centile. Where a significant relationship existed, areas under the Receiver Operator Characteristic curve (AUC) were compared. Doppler parameters’ ability to predict SGA infants, and correlations with neonatal body composition, were evaluated.

Results
Multiple Dopplers were significantly associated with birthweight <10th centile. Of existing parameters, UtA PI performed best (AUC=0.69), followed by the CPR (AUC=0.67). When they were combined as the CPUR, the AUC increased to 0.76. CPUR <0.71MoM demonstrated sensitivities of: 50% for birthweight <10th (90% specificity), 68% for <5th, and 89% for <3rd centile infants; consistently outperforming its constituent parameters. The CPUR demonstrated stronger significant correlations with birthweight centile, Ponderal Index and BF% than the CPR or UtA PI alone.

Conclusion
The CPUR is a novel ultrasound Doppler combination representing the maternal, placental and fetal vasculature in uteroplacental insufficiency. In our cohort, the CPUR is the best Doppler predictor of SGA infants, and demonstrates the strongest correlations with neonatal body composition measures. The CPUR may improve detection of fetal growth restriction.
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Increasing fetal growth velocity increases the risk of shoulder dystocia among non-macrosomic fetuses

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Aim
Shoulder dystocia is a serious obstetric complication. While macrosomia is the most significant risk factor, shoulder dystocia has consistently been found to be an unpredictable event, with 40-60% of all cases occurring in infants with birthweight <4000g¹. The aim of this study was to examine whether non-macrosomic fetuses who demonstrate increasing estimated fetal weight (EFW) or abdominal circumference (AC) centile across the third trimester, are at increased risk of shoulder dystocia.

Methods
EFW and AC centiles were prospectively measured at 28 and 36 weeks in 347 nulliparous women. The change in centiles over exactly eight weeks was calculated. Only livebirths delivered vaginally were included. We excluded cases of EFW >95th centile at 36 week ultrasound, as this is a known risk factor for shoulder dystocia. We calculated the relative risk (RR) of shoulder dystocia for fetuses who demonstrated an increase in EFW or AC of >30 centiles over eight weeks, compared to the rest of the cohort. We also correlated AC and EFW change in centile with neonatal body fat percentage and Ponderal Index.

Results
Of the 347 participants, 39 (11.2%) had EFW >95th centile at 36 weeks and were excluded. Of the 308 participants remaining, 226 (73.4%) delivered vaginally and were included in the analysis, with 6 (2.7%) cases of shoulder dystocia. Increasing EFW and AC centile were both significantly associated with shoulder dystocia. Increasing EFW and AC by >30 centiles over eight weeks were associated with RR of 8.9 (p=0.03) and 7.7 (p=0.02) for shoulder dystocia respectively. Change in EFW and AC centile were also both significantly correlated with neonatal fat measures.

Conclusion
Increasing EFW or AC centile across the third trimester is significantly associated with increased risk of shoulder dystocia in normal weight fetuses. This may assist prediction of shoulder dystocia among non-macrosomic infants.

A Scoping Review of MRI Guided Breast Radiotherapy

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**Aim:** An MRI-Linac integrates a high strength Magnetic Resonance Imaging (MRI) machine and a linear accelerator into a single device. The machine will provide greater soft tissue delineation and real-time imaging throughout a patient's radiotherapy treatment without contributing additional imaging dose. Radiation professionals will be able to treat with greater precision thereby increasing the ability to escalate dose to a tumour and reduce normal tissue side-effects. The aims of this scoping review is to summarise, understand and disseminate findings for the use of an MRI-Linac/Simulator for breast cancer.

**Method:** Computerised searches were performed using Ovid MEDLINE for studies relevant to MRI guided breast radiotherapy. Search terms included breast cancer, MRI-guided radiotherapy, MR Linac/Simulation workflow in publications from 2010 to present. Papers were excluded if metastatic breast cancer was assessed, MRI imaging specific, case studies or non-English articles. Three independent screening of abstracts from EMBASE is currently underway. Relevant full text articles will be retrieved for analysis. Information gathered will be reported according to the Preferred Reporting Items for Systematic Reviews – Scoping Reviews (PRISMA-ScR) system.

**Results:** A total of 5368 abstracts have been identified, of which results to date have indicated that accelerated partial breast irradiation (APBI) may benefit from the integrated machine due to greater visibility of the tumour bed. Margins in this cohort of patients can potentially be reduced enabling favourable short term cosmesis and shorter fractionation. Additionally, contouring of tumour beds in all breast patients will allow for adaptive radiotherapy throughout a patient's treatment. Limitations identified include interactions between secondary electrons generated in the patient and the magnetic field, overall MRI-Linac work flow, quality assurance and MR compatible equipment.

**Conclusion:** This scoping review will provide a foundation of information regarding MRI-Linacs for the treatment and planning of breast patients. The new technology appears to be a promising and feasible treatment option for APBI patients.

**References:**


DCLK1: a novel promoter of gastric cancer progression

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Doublecortin-like kinase1 (DCLK1), a microtubule associated protein (MAP), has recently gained interest in the cancer research field. Whole-genome sequencing suggests that DCLK1 is a novel tumour driver and DCLK1 overexpression correlates with epithelial-to-mesenchymal transition (EMT) in pancreas, intestine and colon cancer. A recent meta-analysis in gastric cancer (GC) showed that DCLK1 overexpression correlates with advanced and poorly differentiated GC, lymph node metastasis and reduced overall patient survival.

Our analysis of the stomach adenomas (STAD) dataset from the Cancer Genome Atlas (TCGA), showed that DCLK1-high expressing tumours significantly clustered within the genomic stable molecular subtype and the histologically diffuse type. We are currently evaluating DCLK1 expression off 300 stomach cancer patients by immunohistochemistry on tissue microarrays.

We established a DCLK1-overexpressing MKN1 gastric cancer cell-line. The overexpression resulted in increased migration and invasion in vitro and in vivo. These findings support our TCGA-STAD data analysis where high DCLK1 levels correlated with EMT, chemokines, and stromal- and immune cell markers. Strikingly, we observed an overall increase in chemokine secretion when DCLK1 is overexpressed, ex vivo. CXCL12 is the one of the main upregulated chemokines; this is further supported by findings in the TCGA-STAD data set, which shows that DCLK1 and CXCL12 expression levels significantly correlate with each other. Furthermore, a DCLK1-inhibitor reversed migration, invasion and chemokine secretion in the DCLK1-overexpressing MKN1 cells to parental MKN1 cell levels, in vitro and in vivo. This suggests that DCLK1 could be a good target for poor prognosis GCs with high DCLK1 levels.

Thus far, the signalling cascade in which DCLK1 can induce EMT or increased chemokine secretion is poorly understood. Our aim is to answer these questions using SILAC mass spectrometry studies by comparing proteomics, phospho-proteomics and secretomics analysis on parental MKN1 and DCLK1-overexpressing MKN1 cells, with and without DCLK1-inhibitor.
Unravelling breast cancer heterogeneity using genetic barcoded patient-derived xenograft

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AIM
Breast cancer is a vast and heterogeneous disease, and it is thought that intra-tumour heterogeneity is responsible for treatment resistance. Therefore, the study of heterogeneity is of great interest for the optimisation of novel combinational therapies.

Methods
The study of tumour heterogeneity is based on new single cell “-omics” technologies now available. However, the caveat of these techniques is that they only represent a snapshot of heterogeneity, at a given time point, often after drug selection. In order to overcome this, we are developing genetic barcoded models using patient-derived xenografts, known to retain the clonal complexity of patient samples. In brief, drug naïve tumours from patients are engrafted in immune-deficient mice and to investigate the fate of transplanted cancer cells, thousands of cancer cells are infected with lentiviruses containing unique genetic tags (or barcodes) that can be integrated into their genome, and transmitted to their progenitors.

Results
We found that primary tumour dissected into pieces harbour a unique barcode repertoire underlying the spatial heterogeneity present in primary tumour. This result has extensive implications for the interpretation of solid biopsies to predict drug response and monitor tumour progression. Interestingly, our results suggest that the cellular features associated with tumour growth and metastases are not random, and we are currently linking the transcriptomic profile of these tumour clones with their phenotypic behaviour.

Conclusion
In this work, genetic barcoding has been elegantly combined with breast cancer patient-derived xenograft to decipher tumour heterogeneity at a cellular level. These new models enabled us to highlight the evolution of a complex clonal landscape during tumour growth and metastatic progression.
Title: Incidence of metastatic disease in low risk Differentiated Thyroid Carcinoma patients.

Authors: Chappell, BM; Lee ST; Scott AM, Department of Molecular Imaging & Therapy, Austin Health

Abstract: Background: 131I-NaI use for remnant ablation in patients who have undergone thyroidectomy for differentiated thyroid carcinoma (DTC) is long established with 85% of DTC patients cured by 131I-NaI therapy surgery in combination with surgery and TSH suppression (1). The presence of distant metastatic disease at initial presentation is low with disease being confined to the thyroid and local lymph glands. (2) Low risk DTC Patient preparation for initial 131I-NaI treatment can use administration of recombinant human thyrotropin-(rTSH) instead of thyroxine cessation to elevate TSH levels. The use of rTSH (Thyrogen®) stimulation followed by 131INaI ablation dose for low risk DTC patients with low clinical suspicion of metastatic disease is standard practice at our institution.

Aim: To determine the incidence of previously undiagnosed metastatic disease in low risk DTC patients undergoing initial Thyrogen® stimulation before 131I-NaI ablation.

Method: A retrospective review was performed on consecutive low risk DTC patients presenting for initial post thyroidectomy Thyrogen® stimulation and 131I-NaI ablation from 2014-2018. Patient demographics, surgery type, histopathology, post ablation imaging results – including thyroid bed uptake and presence of 131I avid metastatic disease were collected. Statistical analysis was performed.

Results: A total of 108 patients with DTC reviewed with a follow up range of 12-61 months. The 131I post ablation imaging results were analysed and the incidence of 131I avid metastatic disease calculated, characterised and possible causal factors investigated.

The incidence of undiagnosed 131I avid metastatic disease in the Thyrogen® low risk patient population was 5.5% (n=6) and 0.9% for distant metastases. Of this metastatic disease group 83% (n=5) of patients had regional lateral lymph node involvement and 1 patient with distant 131I avid bone disease. On follow-up (median = 32.5 month) 50% of these patients had undergone further 131I-NaI Therapy.

Comparison of the metastatic spread patient group to the remaining 94.5% of patients without disease spread identified no specific causal factors for the presence of 131I avid metastatic disease.

Conclusion: 131I-NaI avid metastatic disease in low risk patients is rare and does not contraindicate the use of Thyrogen® stimulation in low risk DTC.

References:
Automated radiosynthesis of \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) on the iPHASE MultiSyn module

Aim:
Prostate-specific membrane antigen (PSMA) is highly expressed in primary and metastatic lesions of prostate cancer.\(^1\) Due to its low abundance in healthy tissues, PSMA allows for highly targeted delivery of therapeutic radionuclide doses with minimal side effects.\(^2\) A number of small molecules targeting the extracellular domain of PSMA with exceptional affinity and specificity have been developed.\(^3,4\) The TheraP study has been designed to investigate the efficacy of the \([^{68}\text{Ga}]\text{Ga-PSMA-11}\) / \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) theranostic pair. For this study, the radiosynthesis and formulation of \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) was automated on an iPHASE MultiSyn radiosynthesizer.

Methods:
Automated radiolabeling of PSMA-617 with Lutetium-177 was optimized on the disposable cassette based MultiSyn. The system was programmed using an Excel based step list and synthesis progression was aided by the built-in radioactivity detectors. Activity losses were tracked using a dose calibrator and minimized by optimizing fluid transfer and cooling steps. \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) was reformulated and sterile filtered using the built-in syringe drives.

Results:
Losses due to residual \([^{177}\text{Lu}]\text{LuCl}_3\) remaining in the isotope vial and the transfer tubing to the reactor were reduced by 55% from 15.0% to 6.7% ± 1.8% \((n = 3)\) and by 94% from 6.6% to 0.4% ± 0.1% \((n = 3)\), respectively. Losses during the recovery of \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) from the reactor were reduced by 83% from 3.0% to 0.5% ± 0.02% \((n = 3)\). Residual radioactivity on the sterile filter and in the manifolds remained constant at 1.2% ± 0.5% \((n = 4)\) and 0.4% ± 0.1% \((n = 3)\), respectively. This resulted in an overall increase in radiochemical yield from 75% to 90.1% ± 0.4% at EOS \((n = 3)\) to give \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) in 96.5% ± 1.1% \((n = 9)\) radiochemical purity (HPLC) after 20 minutes. The content of \([^{177}\text{Lu}]\text{LuCl}_3\) was 1.2% ± 0.8% \((n = 8)\).

Conclusion:
Fully automated production of \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) for clinical use was achieved with minimal exposure to the operator. The cassette-based approach allows for multiple consecutive productions on the same day which will have clinical impact considering the growing number of clinical trials investigating the \([^{177}\text{Lu}]\text{Lu-PSMA-617}\) ligand.

References:
Denoyer D, 1, Kim SH, 2, Redvers RP, 1, Nagpal A, 1, Anderson R, 1 and Pouliot N, 1

New approach to identify and treat patients at risk of breast cancer brain metastasis

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Aim
Brain metastases are associated with an extremely poor prognosis and are incurable. The mechanisms by which breast tumour cells home to and colonise the brain remain poorly understood. Accordingly, identification of predictive biomarkers or therapeutic targets is urgently needed.

Methods
We used gene array profiling to identify novel brain metastasis genes differentially expressed between brain-metastatic 4T1Br4 and parental 4T1 mouse mammary tumours. These analyses revealed 17 genes significantly upregulated in brain-metastatic 4T1Br4 tumours. Limitrin (DICAM), a cell adhesion molecule never previously investigated in the context of cancer, was found to be significantly increased (~12-fold) in 4T1Br4 tumours. We validated these observations at the mRNA and protein level by in silico analyses, immunoblotting and immunohistochemistry (IHC) in a panel of mouse and human cell lines or primary tumours and in a large cohort of tumours from breast cancer patients.

Results
Analyses revealed a strong prognostic association with TNBC and HER2 breast cancer, two subtypes of breast cancer associated with a high propensity to spread to the brain. Highest levels of limitrin were observed in brain-metastatic cells/tumours.
In normal epithelial cells, limitrin interacts with, and modulates the function of αvβ3 integrin, a receptor previously implicated in breast cancer brain metastasis. Its expression is also elevated in brain-infiltrating lymphocytes associated with inflammatory pathologies. Consistent with these observations, we found that limitrin promotes attachment and transmigration of tumour cells across a monolayer of brain-derived endothelial cells in vitro. Further, exogenous expression of αvβ3 in limitrin-expressing TNBC cells increased the formation of intra-parenchymal brain lesions compared to cells expressing limitrin alone which formed predominantly intra-vascular lesions.

Conclusion
Collectively, these results indicate that limitrin has prognostic significance for brain-metastatic breast cancer and contributes to tumour cell crossing of the blood-brain barrier. Experiments evaluating the impact of limitrin suppression on TNBC brain metastasis are ongoing and will be presented.
Characterising the role of IL-36G in the development of gastric cancer

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Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide whereby Helicobacter pylori is a major predisposition which leads to chronic inflammation. There is lack of effective treatments since high recurrence of GC are reported, thus increasing a demand to develop new therapeutic avenues to treat this disease. Our preliminary data indicates that IL-36G expression is elevated in gastric tumours from patients and high IL-36G levels correlate with poorer patient survival. We postulate that IL-36G could be a pro-tumour cytokine which can be targeted as a novel treatment. The aim of this project is to characterise the effects IL-36G elicits on gastric cancer cell proliferation, and whether these pro-tumour effects can be inhibited by its natural antagonist, IL-36RN.

Method

The expression levels of members of the IL-36G family of cytokines were measured by qPCR analysis in three gastric cancer cell lines (GCCs) (AGS, MKN45, MKN1). The effects of IL-36G on GCC proliferation was assessed by colony forming assays. IL-36G signalling can be inhibited by the natural antagonist IL-36RN. Therefore, GCCs were stimulated with IL-36G in the presence of IL-36RN to ascertain if the antagonist can inhibit IL-36G-mediated GCC proliferation. The effects of IL-36G stimulation on ERK phosphorylation in the absence and presence of IL-36RN was also determined by Western Blot.

Results

The mRNA expression levels of IL-36A, IL-36B and IL-36G and its heterodimeric receptors (IL-36R, IL-1RAP) were detected in AGS, MKN45 and MKN1 cell lines. IL-36G mounted a proliferative response at a concentration of 0.1 ng/ml, in comparison to untreated cells. The natural antagonist IL-36RN stimulation was found to inhibit IL-36G-induced colony formation at a concentration of 30 ng/ml. IL-36G was also found to induce ERK2 phosphorylation in GCCs.

Conclusion

Here, we report that IL-36G induces cell proliferation and ERK phosphorylation which can be suppressed by its natural antagonist, IL-36RN. Overall, results from this study provides a solid premise to evaluate IL-36G-based therapeutics for the treatment of GC using in vivo animal studies.
Phenotyping the immune microenvironment in early- and late-stage melanoma

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Aim
Despite the tremendous success of immunotherapy in late-stage melanoma patients, it remains unclear how they affect the immune microenvironment during disease progression. We hypothesise that the immune microenvironment changes across disease stages and is influenced by the differentiation status of tumour cells measured by epithelial-to-mesenchymal transition (EMT). We aim to explore the relationship and correlation between immune cell subsets in melanoma tumours from various stages using multicolour immunohistochemistry (mIHC) and whether EMT contributes to a different tumour microenvironment.

Methods
FFPE tumour blocks from 40 primary and 25 metastatic melanoma tumours were used. All patients were consented under HREC/14/AUSTIN/425. Three antibody panels staining for tumour-infiltrating lymphocytes (TILs), natural killer (NK) cells, dendritic cells (DCs) and EMT markers were optimised for the automated Lecia Bond RX staining processor. Sectioned tissue slides were stained with various marker combinations, scanned using the Vectra® Polaris™ Automated Quantitative Pathology Imaging System, and analysed using the inform software. Different cell fractions were scored against each other across primary/metastatic phenotypes.

Results
A total of 15 antibodies staining for CD4, CD8, CD20, FoxP3, CD68, CD1c, CD141, NKp46, HLA-I, HLA-II, CD3, PD-L1, THBS1 and melanoma lineage were optimised and protocols developed for automated staining. 48 sectioned tissue slides were stained for TIL’s and 36 analysed for TIL phenotypes and numbers. Cell fractions were determined in the tumour region and a high degree of heterogeneity within primary tumours was noted. The limited sample size does not allow for conclusive statistical analyses but enables the detection of trends and effect strength.

Conclusion
This study will provide insight into the co-evolution of the tumour and the immune microenvironment over a given time and reveal processes associated with tumour adaptation to the immune system. This data will lay the foundation for a sufficiently powered follow-up study.
Chi LH,1,2 Burrows AD,1,2 Anderson RL1,2,3,4

BMP4 INHIBITS BREAST CANCER METASTASIS INDEPENDENT OF TUMOUR SMAD4
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4. Sir Peter MacCallum Department of Oncology, the University of Melbourne, Parkville, Victoria, Australia.

Aim

Localised breast cancer is largely curable; however, due to a lack of effective therapies, patients with tumours that have spread (metastasised) have a poor 5-year survival rate at 27%. In our search for therapeutic targets that modulate metastasis, an anti-metastatic protein, bone morphogenetic protein 4 (BMP4), was identified. By ectopically expressing BMP4 in tumours, metastasis can be inhibited in mice. However, BMP4 was reported to promote progression of colorectal and pancreatic cancers. We noted that a critical mediator of BMP4 signalling, SMAD4 (mothers against decapentaplegic 4), is mutated or lost in up to 40% of these cancers, rendering canonical BMP4 signalling defective. In the absence of SMAD4, BMP4 can induce non-canonical signalling through NF-κB and MAPK pathways.

To identify patients who will benefit from BMP4 agonists, we investigated whether the anti-metastatic effect of BMP4 is dependent on SMAD4, and whether detrimental effects can arise from activation of non-canonical BMP4 signalling.

Methods

In human breast cancer MDA-MB-231-HM cells, SMAD4 was reduced with shRNA. In SMAD4-null MDA-MB-468 cells, SMAD4 was ectopically restored. BMP4 was then ectopically expressed in these metastatic lines. Orthotopic tumours were established via injection into the 4th mammary fat pad of NSG mice. Tumours were monitored and resected at 400 mm^3. Subsequent development of metastasis was characterised.

Results

Loss of SMAD4 abrogated canonical BMP4 signalling based on attenuation of target genes (P<0.05). Consistent with our hypothesis, BMP4 accelerated the growth of tumours with low or no SMAD4 (P<0.05) through angiogenesis, while having no effect on those that expressed SMAD4 (P=0.68). Surprisingly, BMP4 significantly inhibited metastasis regardless of SMAD4 expression in tumours (P<0.01).

Conclusion

BMP4 inhibits breast cancer metastasis independent of tumour SMAD4, but promotes the growth of SMAD4-low tumours. We are testing small molecule agonists as a therapy to treat metastatic breast cancer and to improve patient survival.
Investigating the role of GP130/STAT3 signalling in intestinal barrier function

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Aim
Colorectal cancer (CRC) is the third most common fatal malignancy worldwide, with 40-50% patients dying from this disease. As its prevalence continues to rise, advances in treatments are urgently needed to alleviate the morbidity and mortality associated with CRC. The intestinal epithelium provides a physical and biochemical barrier against commensal and pathogenic microorganisms. Perturbations in barrier function promotes chronic inflammation, which can drive tumorigenesis and alter responsiveness to anti-cancer therapies. The Signal Transducer and Activator of Transcription 3 (STAT3) is a key driver in the progression of inflammation-associated CRC. However, the role for STAT3 in intestinal barrier function is yet to be delineated. Here we study the role of STAT3 in intestinal barrier function during chemically-induced colitis.

Method
We utilised two different mouse models to partially ablate STAT3 protein or genetic expression in vivo. One mouse model harbours a truncated GP130 receptor (GP130ΔSTAT+) to reduce GP130-dependent STAT1/3-mediated activation. The second mouse model carries a Doxycycline-inducible Stat3 short-hairpin RNA (shSTAT3) for the reversible genetic silencing of Stat3. These mice were then challenged with the chemical irritant Dextran Sulfate Sodium (DSS) and intestinal barrier function was assessed using an in vivo FITC-dextran permeability assay. Colonic tissues were harvested and analysed via qRT-PCR and western blotting.

Results
We demonstrate that partial STAT3 deletion significantly increases the susceptibility to DSS-induced colitis, indicated by i) decreased intestinal barrier function, ii) severe weight loss and iii) histological damage. We further identify that reduced barrier function is accompanied by altered expression of the Reg3b and Reg3g antimicrobial genes, as well as reduced expression of the tight junction Claudin proteins.

Conclusion
Together, our data suggest STAT3 activity is essential for the maintenance of intestinal barrier function. Therapeutically targeting the GP130/STAT3 signalling cascade in intestinal epithelial cells, and selectively manipulating barrier function, may pose as a potential strategy to alter responsiveness to chemo- and immuno-therapy in CRC patients.
Selective Stat3 inhibition in the tumour microenvironment restricts gastrointestinal tumour growth

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Aim
The signal transducer and activator of transcription 3 (STAT3) is key a transcription factor often found to be overexpressed in tumours, and is associated with the development of cancer hallmarks such as sustained proliferation and avoidance of cell death. Indeed, the pro-tumorigenic role of intrinsic Stat3 signalling within tumour cells is well characterised across a number of different cancers including gastrointestinal cancers. However, the influence of Stat3 among the non-tumour cells that infiltrate the tumour microenvironment is less explored. This project aims to elucidate the role(s) of STAT3 in the non-tumoural compartment of the tumour microenvironment.

Methods
We developed the shStat3 transgenic mouse that allows for the conditional knock-down of STAT3. The shStat3 was crossed with the gp130F/F mutant gastric cancer mouse. The shStat3 mice were also injected subcutaneously with MC38 murine colon cancer cells. Variations of this model were used for bone marrow chimera experiments, and testing with the Stat3 inhibitor BBI-608. Tissues from these experiments were subjected to protein and RNA analysis by western blot and q-RT-PCR respectively. The immune-profiles of the excised tumours were also interrogated by FACS analysis.

Results
Systemic Stat3 reduction in the gp130F/F mice decreased tumour burden. Importantly, Stat3 knockdown in the non-tumoural compartment alone significantly inhibited allografted-MC38 tumour growth. Bone marrow chimera experiments confirmed the hematopoietic compartment as the main drivers of this anti-tumour effect. Furthermore, an increase of monocytic (Ly6C⁺Ly6G⁻) cells were observed in Stat3-knockdown allografts, an affect recapitulated with pharmacological Stat3 inhibition. The Stat3-knockdown monocytes exhibited reduced immunosuppressive gene signature expression.

Conclusion
Our data provides compelling evidence of the therapeutic value of specific Stat3 targeting as a novel therapy option against gastrointestinal cancers. Strikingly, the anti-tumoural responses were shown to be partially mediated through immune cells such as the monocytes, highlighting a key role for the immune environment in the responsiveness to anti-Stat3 therapies.
Title: Determining the effect of bazedoxifene in combination with chemotherapy on colon cancer cells

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Abstract

Inflammatory cytokines, such as interleukin-6 (IL-6) and IL-11, activate the signal transducer and activator of transcription 3 (STAT3), which drives the gene transcription of cellular processes attributed as hallmarks of cancer. High levels of these cytokines, in combination with driver mutations, facilitate tumour growth and progression in preclinical models of colon cancer. Previous studies in our laboratory identified bazedoxifene (BZA), currently approved for the treatment of osteoporosis, as a small molecule inhibitor of GP130 (the receptor common to the IL-6 family of cytokines), selectively suppressing IL-6 and IL-11 signalling to reduce colon and gastric cancer growth in vivo (Thilakasiri et al. EMBO Mol Med 2019).

The specific aims of the current study are to determine (i) the effects of BZA in combination with chemotherapy on apoptotic pathways in colon cancer cells and early passage patient derived colon cancer cells; (ii) the effects of BZA in combination with chemotherapy on apoptotic body formation in colon cancer cells and (iii) identify new compounds that inhibit GP130 activity. The combined effect of BZA, fluorouracil and oxaliplatin on inducing apoptosis in LIM2405 colon cancer cells was analysed using flow cytometry. STAT3 expression and response to IL-11/STAT3 signalling was characterised by Western blotting. An in silico screen of GP130 using a small molecule library was conducted and compounds were tested for effects on STAT3 transcriptional activity using cell-based assays.

Our results demonstrated that combination treatment with BZA, fluorouracil and oxaliplatin significantly increased apoptosis in LIM2405 cells. We have also identified novel analogues of our lead small molecule compound which decrease STAT3 transcriptional activity. Our data showed that BZA inhibited GP130-dependent STAT3 activity in the human colon cancer cell line LIM2405. BZA treatment sensitized cells to chemotherapy leading to increased apoptosis. The identification of novel compounds that target GP130 suggests a role for STAT3 inhibition in colon cancer as a treatment strategy.
Riley J Morrow¹,², Robert O'Donoghue¹,², Ashleigh Poh¹,² and Matthias Ernst¹,²

Therapeutically targeting Myc in gastric cancer

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Background:
Myc is a critical regulator of gastric tumour development and progression, and is associated with a poorer survival rate in human gastric cancer patients. Hyperactivation of inflammatory signalling cascades, including the Jak/Stat3 pathway, is crucial for gastric cancer development and can result in the overexpression of Myc. However, the pro-tumorigenic role of Myc in gastric cancer remains poorly understood.

Aim:
Previous findings from our lab using the Gp130FF mouse model, which spontaneously develops gastric adenomas through IL-11 dependent hyperactivation of Stat3, identified an upregulation of Myc in these tumours. Here, we investigate the cellular requirement of Myc in gastric tumourigenesis by genetically ablating Myc within gastric epithelial cells. As well, we explore the therapeutic benefit of reducing the transcriptional activity of Myc through the use of the small-molecule inhibitor IBET-151.

Methods:
Tumour-bearing Tff¹CreERT²;Mycfox;Gp130FF mice were treated with tamoxifen for 3 days and/or IBET-151 for 21 days. At the experimental endpoint, tumour weights were recorded and tissue collected for biochemical analysis.

Results:
Genetic ablation of Myc in gastric epithelial cells significantly reduced tumour growth and activation of Jak/Stat3 signalling, as observed by decreased phosphorylated Stat3. Immunohistochemical analysis revealed a significant reduction in the percentage of Ki67+ proliferating cells. RNA-Sequencing of whole tumours subjected to KEGG pathway analysis similarly demonstrated a significant downregulation of cell-cycle related genes.

Therapeutic inhibition of Myc using the small-molecule inhibitor IBET-151 also significantly impaired tumour growth, consistent with a reduction in Myc, demonstrating its therapeutic benefit in this gastric cancer mouse model.

Conclusions:
Excessive Myc activity in epithelial cells promotes gastric cancer development and progression by enhancing tumour-cell proliferation. Future work will identify the underlying mechanisms by which IBET-151 similarly impairs gastric tumour growth. Taken together, our results suggest that inhibition of Myc may be a promising therapeutic target for the treatment of gastric cancer patients.
Targeting Tuft cells and Innate Lymphoid Cells in Gastric Cancer

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Aim
Gastric cancer is the third leading cause of cancer-related deaths, and accounts for 900,000 deaths annually. Tuft cells are a rare subset of mucosal epithelial cells that are significantly increased during gastric tumorigenesis, and serve as a major source of IL25 within the tumour microenvironment. The production of IL25 promotes the activation of type 2 Innate Lymphoid Cells (ILC2s), and results in a feed-forward loop that promotes tuft cell development through the IL25/IL13 signal transduction pathway. Here we assess the therapeutic potential of targeting tuft cells and ILC2s during gastric cancer.

Methods
To better understand the role of tuft cells and ILC2s in gastric tumour progression, we utilized the Gp130F/F mouse model of spontaneous intestinal-type gastric cancer to assess tuft cell and ILC2 numbers. To study the therapeutic benefit of targeting tuft cells and ILC2s interactions, we genetically ablated tuft cells in treated tumour-bearing Gp130F/F mice or treated them with a neutralising anti-IL25 antibody.

Results
We observed a significant increase in tuft cells and ILC2s in the blood and gastric tumours of Gp130F/F mice compared to wild-type (WT) controls. These results were consistent with increased Il13 and Il25 gene expression in Gp130F/F tumours compared to WT tissue. Accordingly, tuft cell ablation significantly impaired tumour growth and ILC2s in Gp130F/F mice, and reduced Il13 and Il25 gene expression within tumours.

Likewise, anti-IL25 treatment in Gp130F/F mice lead to significantly smaller tumours and reduced tuft cell numbers in these mice. In vitro analysis of gastric tumour organoids similarly demonstrated that treatment with anti-IL25 suppressed tumour organoid growth, while stimulation with IL13 enhanced organoid growth.

Conclusion
Together, our results suggest tuft cells and ILC2s form a positive feed-forward loop that drives gastric tumour development through an IL25/IL13 signalling cascade. Inhibition of this pathway therefore provides a promising therapeutic approach for the treatment of gastric cancer.
Title: “Seeing the Opportunity”

Background:

Our Palliative Care Unit (PCU) had 553 deaths in 2017 however, only 11 eye donations occurred.

Many patients and families find the opportunity to restore sight in others a fulfilling outcome.

Barriers to donation were identified as:

- Lack of staff knowledge regarding process involved
- Misconceptions around eligibility and exclusion criteria
- Low confidence levels in conducting the donation conversation

Aim:

To increase number of eye donations within the palliative care unit and to improve staff confidence in discussing eye donation with families.

Methods:

- Staff surveyed to establish understanding of and barriers to donation
- Attended education sessions provided by “Donate Life”
- Tour of “Lions Eye Donation Service”
- Education sessions held on eye donation
- Screening tool created and introduced to identify all eligible patients
- 1:1 staff training provided on facilitating eye donation
- Ward donor register developed, allowing patient’s donor status to be identified and communicated to staff and families

Results:

Since the introduction of the screening tool in June 2018, screening each patient for eye donation eligibility is now standard practice in PCU, resulting in:

- 36 corneal donations from PCU in 2018 and 39 so far in 2019 (11 in 2017 pre screening tool)
- Austin Health now the leading hospital for corneal donors in Victoria with 91% coming from PCU
- Since introducing the screening tool, 627 deaths occurred, of those 237 were eligible, 137 were offered donation and 75 consented
- 36 registered donors were identified and of those 32 consented
- Reduction in missed potential donors - January to June 2018 (pre introduction of screening tool), there was 117 missed potential donors; this number reduced to 43 from June to December 2018 once the tool was launched. In the period of January to June 2019 there has only been 9 missed potential donors, 6 of these have been due to family aggression.
- Sight has been restored in 125 people since June 2018.

Conclusion: Staff education and routine patient screening dramatically increased donation rates.
Title of Abstract: Introducing Mindfulness as a Self Care tool in the Palliative Care Unit (PCU)

Juli Moran, Hilary Hodgson

Background:
The Austin Palliative Care Service has changed considerably in the last 5 years, moving from the sub-acute campus into a new purpose built facility on the acute site. There has been a doubling of admitted patients, a decrease in length of stay and an increase in patient acuity. Patient and carer expectations have also increased significantly.

In 2017 a winter strategy was to increase the PCU beds by 33% to 28 beds. This resulted in an increase in deaths per week, averaging 15 per week and peaking at 20 per week.

Whilst the staff are very resilient and have developed their own self care plans, it was identified that introducing them to mindfulness as a self care skill would be beneficial to both their work and personal life.

Aim
The aim was to provide palliative care staff with the opportunity to learn and develop mindfulness skills to assist them with their overall wellbeing.

Methodology
A block of six sessions in a one-hour format were offered to all staff. At the session skills in meditation and yoga nidra are introduced allowing participants to set their own goals and work towards their own goals eg stress reduction.

Results
A program evaluation via a staff survey was undertaken. Questions relating to helpfulness of sessions, the staff ability to practice their new skill and any barriers to practice identified will be shared.

Conclusions
We aim to demonstrate the effect of a mindfulness program on the well-being of acute palliative care unit staff.
What a difference more beds make!

Hilary Hodgson, Juli Moran, Helen Longton

Background: The Austin Palliative Care Unit (PCU) is a 21 bed unit based at an acute tertiary hospital. As part of our hospital Winter strategy an extra 7 beds were opened from April to October 2018.

Aim: To describe the impact on hospital flow and the PCU workload with a 30% increase in bed numbers.

Method: Specific Key Performance Indicators (KPI) were set by the palliative care staff and executive to determine the impact of the additional beds on hospital flow and PCU performance. Data was tracked monthly, with a formal report at the end of the period. Regular monitoring with staff was undertaken.

Results: There was a 48% increase in referrals and 59% increase in admissions. There was a dramatic increase in admissions from the intensive care and emergency departments due to the increased availability of beds. There was a reduction in waiting time for all referrals. The only KPI that was not met was a 20% increase in direct admissions from the community (10% increase seen). There were multiple challenges related to rapid increase in staffing, faster turnover of patients and lack of equipment and space on the ward.

Conclusion: The increase in bed numbers produced a significant improvement in access to the PCU although there were several challenges that needed to be overcome. As a result of the success of the increase, funding for additional permanent beds was provided, and it is expected that 28 beds will again be offered during the winter peak.
Influence of an Early Stress-reduction Intervention for Very and Extremely Preterm Infants on Behavioural, Cognitive and Academic outcomes from 2 to 9 Years of Age

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Aim
The landmark findings of the Mother-Infant Transaction Program (MITP) showing improved neurodevelopment of preterm infants following parent-sensitivity training in the neonatal intensive care unit have been inconsistently replicated. This study evaluated outcomes from an MITP-type intervention to school age.

Methods
A randomised controlled trial involved 123 very preterm and extremely preterm infants allocated to either a parent-sensitivity intervention (PremieStart, $n = 60$) or to standard care ($n = 63$). When children were 2 and 4.5 corrected age, parents completed the Child Behavior Checklist. General development was assessed at 2 years with the Bayley Scales of Infant Development. At 4.5 years, cognitive functioning was assessed with the Wechsler Preschool and Primary Scale of Intelligence and executive functioning with the NEPSY-II. The children’s cognitive assessment was replicated at 6.5 years and Grade 3 NAPLAN results were collected when they were approximately 9 years of age (results are currently being analysed).

Results
There were no significant between-group differences in behaviour problems at 2 or 4.5 years, general development at 2 years, or cognitive and executive functioning at 4.5 years.

Conclusion
Despite promising findings in infant communication at an earlier time point, this cohort has not shown sustained improvement. It is possible that advances in the quality of neonatal intensive care may mean that MITP-type interventions now have limited additional impact on preterm infants’ long-term neurobehavioural outcomes. We included infants with a gestational age (GA) < 30 weeks (mean GA 27 weeks) including extremely preterm infants. The intervention may have decreasing benefit for children born at successively lower GA. The timing of intervention may also have affected its efficacy. It is vital that researchers continue to publish the full, long-term outcomes of MITP-type trials or place them in open access repositories, in order that the evidence base can be collectively assessed without bias.
Brotto J ¹, Grabsch EA ², Leroi ML ²

Simplification of Direct MALDI-TOF Identification from Positive Blood Culture Broth

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Aim  
Evaluation of Matrix-assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF) using saponin lysis and pre-warmed short-incubation chocolate blood agar (pCBA) methods for rapid identification of positive blood culture (posBC) isolates. A simple direct method (from posBC broth) using saponin lysis has the potential to reduce turn-around times (TAT) for reporting posBC isolates, with minimal impact on laboratory workflow.

Methods  
PosBC broths were subcultured on pCBA (manually), and standard culture media (automated BD Kiestra system). Direct broth saponin-lysis method was performed by adding 1 ml of posBC broth to 200 µl 5% saponin, vortexing for 1 minute, centrifuging for 1 minute), resuspending the pellet in 1 ml deionised water, and then re-centrifuging the suspension. The final spun-pellet was spotted onto 4 target wells (each with 70% formic acid) on a MALDI-TOF slide. pCBA short-incubation subcultures were checked for growth at 2, 3 and/or 4 hours. MALDI-TOF (4 wells each with formic acid [BioMerieux]) was performed from pCBA when visible growth was present. Results of both early identification methods were compared to MALDI-TOF identification from standard culture media at 18-24 hours. All MALDI-TOF testing was performed on Vitek-MS (Biomerieux).

Results  
Overall, 227 mono-microbial and 20 poly-microbial posBC were analysed. In the mono-microbial posBC group, saponin lysis was concordant with 24-hour MALDI-TOF in 92/158 (58%) Gram-Positive (GP) and 49/58 (85%) Gram-Negative (GN) culture samples. pCBA concordance rates were 85/158 (54%) and 45/58 (78%) for GP and GN posBC respectively. 2/227 (2.2%) of isolates were misidentified using saponin lysis, and none with pCBA. Labour time for saponin lysis was 7.4 min compared to 4.5 min for pCBA. Notably, results using the saponin method were available 2-4 hours earlier.

Conclusion  
Saponin-lysis identification rates were comparable to pCBA rates but resulted in earlier notification of results, with expected benefits in patient management and anti-microbial stewardship.
Benchmarking Blood Culture Turnaround Times at Austin Pathology

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Aim
Positive-blood culture turnaround times (BC-TATs) for Austin Pathology Microbiology Laboratory (AuPath-Micro) were compared against recently published benchmarks for microbiology laboratories (with/without automated systems) for reporting; Gram stain (GS), organism identification (Org-ID) and antibiotic susceptibility testing (AST). Blood cultures (BCs) detect blood-borne bacteria/fungi that may be causing an infection with serious and life threatening implications. Rapid and proficient (BC) results are essential in providing best patient outcomes and reducing hospital-associated costs.

Methods
AuPath-Micro utilises advanced technology to standardise specimen/culture processing and improve workload efficiency. Technology/automation includes Bactec-FX BC-System, Kiestra-Automation, mass spectrometry (MALDI-TOF) identification and automated antimicrobial-susceptibility (Vitek2-XL). BCs collected January-February 2019 from Austin Health patients (N=7838 bottles, 3976 requests, 1391 patients; 508/7838 [6.5%] positive) were reviewed. Detailed analysis of all first positive bottles (n=220, 184 patients) was performed, as these results have the most impact on patient management and are given highest priority.

Results
The median (Interquartile Range [IQR]) BC-TATs (hours from BC collection) to GS, preliminary results for Org-ID and AST were 21.1 (14.9-31.2), 24.2 (19.2-36.0) and 36.0 (32.9–43.4), respectively. Similarly, final-results for Org-ID and AST reporting were 35.3 (27.1-46.6) and 49.4 (40.3-65.3). Respective benchmark results (in hours) for non-automated and automated laboratories were GS 19.2 (15.4-25.9), 19.2 (14.6-28.3); final Org-ID 43.4 (32.2-59.0), 36.0 (22.3-43.7); final AST 65.0 (59.0-71.8), 60.0 (45.4-73.0). Unlike AuPath-Micro, both laboratories reported GS results 24/7. GS BC-TATs during AuPath-Micro business hours (BH) were 18.7 (13.4-26.6) and after hours (AH) 23.3 (19.0-37.7). During BH AuPath-Micro reported BC-GS TATs 0.5hrs earlier than the benchmark. Facilitated by Kiestra-Automation and standardised incubation, final Org-ID and AST are set up where possible using 6hr subcultures from positive-BCs, potentially explaining rapid BC-TAT.

Conclusion
AuPath-Micro performs well against published benchmarks for ID and AST of positive-BC. Further method development and monitoring of BC-TATs will ensure that rapid and proficient reporting of BC results is ongoing.
Automated Resistance Detection: Comparison of BD Phoenix to bioMérieux Vitek 2 for Susceptibility Testing of Multi-drug Resistant Isolates

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Objective: There is a lack of literature comparing the performance of the BD Phoenix M50 (PHX) with the Vitek 2XL (V2) system in susceptibility testing of multidrug resistant organisms. We evaluated the accuracy, reliability and reproducibility of these systems using a collection of organisms with confirmed resistances (molecular +/- phenotypic).

Methods: The PHX NMIC-404 and PMIC-84 panels and the V2 AST-N246 and AST-P612 cards were tested for analytical reproducibility across different organism categories. 10 ATCC organisms, 200 Gram negative bacilli (GNB) and 100 Gram positive cocci (GPC) were used in this study. Isolates were tested simultaneously on both platforms and minimum inhibitory concentration (MIC) values of antibiotics common to both systems compared. Organisms with >1-fold difference in MIC had broth microdilution (BMD), (Thermo Fisher Sensititre panels GN3FG- and GPALL1FG+) performed as a reference standard.

MIC data was compared across the instruments and analysed by MIC and categorical interpretation (CLSI standards). MIC measurements were classified as concordant (EA – essential agreement) if MIC results were within 1 dilution of each instrument, while categorical interpretation was classified (CA – category agreement) using standard definitions of susceptibility errors (minor (mD), major (MD) and very major discrepancies (VMD).

Results: 10 ATCC strains each tested 5 times found 100% EA on both instruments. For the 200 GNB tested, overall EA and CA were 95.8% and 90.7%, respectively. 50.5% of isolates required BMD to resolve discrepancies. The VMD, MD and mD rates were 0.16%, 0.48%, 1.18% and 0.29%, 0.61%, 1.09% for PHX and V2, respectively. The antibiotic with highest percentage of discrepant MICs overall was cefepime with an EA and CA of 79% and 65.5%.

Relative discrepancies were low for GPC, the overall EA and CA was 95.0% and 94.7%.

Conclusion: The performance of both systems was comparable with a low level of VMD and MD. Evaluation of a resistant population revealed generally acceptable results similar to more susceptible populations.
Automated Resistance Detection: Comparison of the expert systems of BD Phoenix and bioMérieux Vitek2 for Susceptibility Testing of Multi-drug Resistant Isolates

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Objective:
The rising incidence of multidrug resistant organisms has made interpretation of antibiograms more challenging for Microbiologists. Assistance through use of interpretive algorithms in automated platforms such as the Vitek® 2XL has been valuable. The comparative performance of these systems has not been well documented. The expert systems (ES) of the BD Phoenix M50 (PHX) and the Vitek 2XL (V2) was tested against a collection of organisms with confirmed resistances (molecular +/- phenotypic).

Methods:
Isolates were tested simultaneously on both platforms. The instruments interpretation of resistance mechanisms was evaluated based on the ability to accurately classify a number of key resistance mechanisms including extended spectrum β-lactamases (ESBL), acquired AmpC β-lactamases (AmpC), carbapenem resistant Enterobacteriaceae (CRE), vancomycin resistant Enterococci (VRE), glycopeptide non-susceptible Staphylococci and MRSA (Methicillin resistant Staphylococcus aureus).

Results:
From 200 Gram negative bacilli tested, there were 158 isolates which harbored 178 designated acquired resistances. For specificity, 42 isolates were included that had no acquired resistance mechanisms detected either phenotypically or genotypically. The sensitivity for the ES corresponding to the reference genotype/phenotype was (PHX 90%, V2 77%), although the error rate was higher when analysed as a proportion of total tests (PHX 91%, V2 78%).

100 Gram positive cocci were tested. For 30 VRE, the sensitivity of the ES to correctly classify vanA & vanB was 100% for both systems, for low MIC vanB, the sensitivity was 30% for PHX and 10% for V2, however the limitation of the PHX system was its inability to differentiate between vanA & vanB. Both ES were able to correctly classify methicillin resistance across the variety of Staphylococci tested. The sensitivity of the V2 ES to alert to possible hVISA/VISA was 53.3% compared to 0% on the PHX.

Conclusion: The performance of the ES was difficult to compare due to different levels of sophistication of the reporting algorithm, however, the V2 had superior performance, with a greater specificity. Both systems were designed to maximise sensitivity and should be considered screening algorithms only.
A Comparative evaluation of Cepheid GeneXpert® and BD MAX™ Enteric Viral panel for the detection of Norovirus in faeces.

Department of Microbiology¹, Austin Health

AIM

This study involves comparative evaluation of Cepheid Xpert® Norovirus Real time PCR and BD MAX™ Enteric Viral Panel assay against Primer Design genesig assay.

Norovirus is a highly infectious virus with low infective dose known to cause outbreaks of acute gastroenteritis, across various institutional settings such as hospitals and aged-care facilities.

The current diagnostic method at Austin pathology involves Primer Design genesig kit for Norovirus genotypes I and II which has decreased sensitivity and slower turn-around time in comparison to many commercial assays.

METHODS

50 unformed and unpreserved faecal samples from patients with symptoms of acute gastroenteritis were run in parallel on Cepheid Xpert® Norovirus PCR, BD MAX™ Enteric Viral Panel and compared against Primer Design genesig. 10 known positive samples underwent further 2 log10 dilutions to check for analytical sensitivity. Any discrepant results were retested.

RESULTS

In total, 15 samples tested positive out of which 10 samples underwent 2-log10 dilutions. All 10 samples tested positive on further dilution and 9/10 samples showed linear progression of Ct values. One sample gave false negative result on BD MAX™ on the neat specimen, though on repeat testing gave positive result with higher Ct value.

CONCLUSION

A 100% concordance were noted between all three assays. Both kits were easy to use but Xpert® was quicker at sampling by a minute and the overall runtime faster by an hour. Xpert® also had the advantage to be able to distinguish between genotypes I and II.

Both BD MAX™ and Xpert® demonstrated similar performance. The one false negative result initially observed on BD MAX™ could be due to sample being on the cut-off for limit of detection in this assay. The Ct values on some samples on BD MAX™ also did not produce a direct relationship with dilution but could still detect viral RNA.

This comparative evaluation has demonstrated that both the assays accurately detect Norovirus from stool samples, and both fit for purpose in replacing the Primer Design genesig assay.
Slow-release opioids post surgery: what messages are patients receiving?

Background

The use of slow-release opioids for acute pain has been under scrutiny since the release of the ANZCA position statement in 2018. Despite a lack of supporting evidence, prescribing slow-release opioids has been traditional practice following surgery at our institution; a large tertiary Victorian public hospital. Some reasons for this may include facilitating post-operative mobility, reducing length of hospital stay and an extrapolated benefit drawn from chronic pain practices.

At our institution, clinical ward pharmacists review all discharge prescriptions. Special instructions regarding intended duration and follow up advice are often communicated on dispensing labels and medication lists.

Aim

The aim of this retrospective audit was to assess the completeness and consistency of information provided to patients upon discharge from pharmacists, review the documentation of follow-up plans conveyed to general practitioners from hospital prescribers and evaluate the appropriateness of slow-release opioids quantities when discharged post-surgery based on local guidelines.

Methods

Patients discharged with a slow-release opioid following inpatient surgery during October 2018 were included in the study and retrospectively recruited utilizing pharmacy dispensing software. Data evaluated was obtained from electronic medication charts and discharge summaries, departmental pharmacy dispensing history and archived medication lists.

Results

227 patients were included in the study equating to 275 slow-release opioids prescribed. 211 of these (77%) were new, for which 58% had clear end dates or follow-up instructions documented by discharge pharmacists. Although there were 201 (95%) completed discharge summaries, 58% contained no information regarding follow-up plans for local practitioners and 23% simply stated “weaning analgesia”. Only 18% discharge summaries had clearly documented slow-release opioid plans, whilst 15.1% did not have any discharge summary.

Conclusion

Our study has demonstrated that patients and community prescribers are not consistently provided specific information about when to stop or review slow-release opioids after surgery.
Compliance with hospital guidelines for antipsychotic prescribing in the management of delirium: a retrospective audit

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Background

Delirium is a common complication that may prolong length of hospital stay and worsen patient outcomes. At Austin Health, delirium guidelines assist prescribers in making appropriate treatment choices, including use of non-pharmacological management as first-line treatment, minimising unwarranted use of antipsychotics, obtaining consent for antipsychotic use, selecting appropriate antipsychotic doses and monitoring for adverse effects.

Aim

To assess compliance with Austin Health guidelines when prescribing antipsychotics for patients with delirium.

Methods

Data was obtained about patients admitted to Austin Health between 15/02/19 and 14/04/19, diagnosed with delirium and given an antipsychotic medication. Patients who were taking an antipsychotic medication prior to admission, prescribed an antipsychotic for indications other than delirium or prescribed an antipsychotic during end-of-life care, were excluded. Prescribing data was collected from Cerner. Compliance with the guidelines was evaluated from patient notes in Cerner and Scanned Medical Records.

Results

Thirty patients met the inclusion criteria (median age 78 years). Fourteen (46.6%) patients met the criteria for prescribing an antipsychotic (distressing symptoms despite implementation of non-pharmacological management or evidence of imminent risk of harm to patient or others). Two (6.7%) patients had documented evidence that the patient or family were consented or informed about antipsychotic treatment. Only one patient received all recommended monitoring during treatment. Eight (26.7%) patients received a starting dose that was consistent with guideline recommendations taking into consideration advanced age (≥70 years) and frailty (FI-LAB score ≥0.3).

Conclusion

Documentation supporting the decision to prescribe an antipsychotic medication for delirium was lacking for more than 50% of patients. There was little evidence that patients or their families were informed or consented when antipsychotic medications were prescribed. Antipsychotic starting doses often exceeded guideline recommendations. These findings highlight a need to improve adherence to Austin Health delirium guidelines and documentation when prescribing antipsychotics.
Measuring peak cough flow in the clinical setting: an evaluation of devices and interfaces

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Aim
Peak cough flow (PCF) is used as a measure of cough effectiveness, especially in people with neuromuscular disease (NMD) and routine measurement of PCF may aid clinical assessment. Unlike other respiratory function tests, there are no standardized methods for measuring PCF in healthy or NMD-affected populations. The aim of this study was to compare PCF between different devices and interfaces.

Methods
Experiment 1: Forty healthy participants performed three coughs, at two effort types ("maximal" and "weak"), into three devices: i) EasyOne Spirometer (PCFEO), ii) Peak Flow Meter (PCFPFM) and iii) pneumotachometer (Hans Rudolph™ Model 3700A)(PCFPN). Devices were connected in series and testing and effort order were randomized.

Experiment 2: Forty healthy and NMD affected participants each performed three coughs into i) PCFEO using a mouthpiece (PCFMP), and ii) oro-nasal facemask (PCFONM), with the order of interface randomized.

Results were analysed using paired t-tests and Bland and Altman analyses.

Results
Experiment 1: Five hundred and forty coughs were sampled (PCFPN range =18.49 - 535.2 L/min). Thirty-five “weak” coughs were not detected on the EasyOne spirometer (n=17) or the Peak Flow Meter (n=18). Of the remaining paired data, PCFPN was significantly higher than PCFEO, with a mean (95% Limits of agreement) bias of -6.75L/min (-50.00 to 36.50), p < 0.001. There was no significant difference between PCFPN and PCFPFM (-1.56L/min (-26.15 to 23.02, p=0.114)).

Experiment 2: On average, the PCFMP was significantly greater than PCFONM (15.075 ±30.02 L/Min, 95% CI, 2.98 to 27.17, p=0.01,) in healthy participants, however there was no difference in participants with NMD (-1.0 ±41.29 L/Min, 95% CI, -13.35 to 12.24, p= 0.93).

Conclusion
PCFPFM demonstrated high agreement with the PCFPN. Although PCFEO produced statistically different readings, the mean bias was not considered clinically important. PCFMP reports higher cough strength than a PCFONM in healthy individuals but no significant difference in NMD. This has clinical implications as both interfaces could potentially be used reliably in NMD population.
Pneumothorax in neuromuscular disease associated with lung volume recruitment and mechanical insufflation-exsufflation.

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Aim:
To describe two cases of pneumothorax associated with lung volume recruitment and mechanical insufflation-exsufflation in neuromuscular disease and review the literature on incidence and risk factors.

Methods:
The medical records of two patients with pneumothorax and neuromuscular disease were reviewed. Keywords from each case informed a literature search. Published databases searched included: MEDLINE, EMBASE and the Cochrane Library.

Results:
Case 1: A 25-year-old male with Duchenne muscular dystrophy presented to the emergency department with chest pain and dyspnoea secondary to a large right-sided pneumothorax. Onset of symptoms began following prolonged use of mouthpiece intermittent positive pressure ventilation and multiple sessions of mechanical insufflation-exsufflation. Case 2: A 71-year-old male with motor neurone disease presented to the emergency department with worsening dyspnoea and chest pain immediately following lung volume recruitment therapy. Chest radiograph revealed a large right-sided pneumothorax.

Literature Review: The minimum prevalence of patients with neuromuscular disease on home mechanical ventilation is estimated at 3 people per 100,000. Within this population, few cases of pneumothorax have been published, suggesting this complication likely rare. Additionally, there is no published data identifying lung function thresholds or respiratory system compliance values for which the risk of pneumothorax secondary to lung volume recruitment or mechanical insufflation-exsufflation increases. Given the probable rarity of this complication, it is unlikely that robust measures for risk of pneumothorax can be developed and prospectively validated. As such, clinicians are required to make a judgement based on the patient’s primary pathology, comorbidities, disease trajectory and ability to perform the techniques safely.

Conclusion:
The presence of prior pathology is a precaution that warrants careful consideration when prescribing lung volume recruitment or mechanical insufflation-exsufflation. However in cases where no established risk factors exist, clinicians may need to consider the goals of therapy and educate patients on the risk versus benefit.
Sheers N,1,2,3 Berlowitz DJ,1-4 Rochford P,1,3 Dirago R,1,4 Naughton P,1 Henderson S,1 Howard ME.1,2,3

Respiratory function and infections in people with motor neurone disease

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Background

Respiratory complications are the primary cause of death for people living with motor neurone disease (MND). Our understanding of respiratory physiology however, comes largely from studies of people with slowly-progressive neuromuscular disease (NMD), not rapidly-progressive disease like MND. Furthermore, the rate of respiratory tract infections (RTI) is not well established, with between 9-75% reported in MND. Thus, study aims were to compare respiratory function and history of RTI in people with MND compared to those with other NMDs.

Methods

Vital capacity (VC), peak cough flow (PCF), lung volumes, maximal inspiratory and expiratory pressures (MIP, MEP) and total respiratory system compliance (Crs) were measured in 27 community-dwelling participants with MND and 53 people with other NMDs. A priori comparisons of respiratory function were made by disease type (MND or Other)(Student’s t-test) and RTI history in the previous year (Fisher’s exact test for proportions).

Results

Respiratory muscle strength was not significantly different between groups (MND vs Other, mean±SD: MIP 39±19% vs 47±28% predicted, MEP 40±19% vs 44±23% predicted). The VC was higher (53±15% vs 35±17% predicted, p<0.01) and the chest less stiff (Crs 0.041±0.027 vs 0.023±0.020 L/cmH₂O) in people with MND. History of RTI was associated with lower VC and PCF, and fewer people with MND reported RTIs (22% vs 53%, \( p=0.010 \)).

Discussion

In this exploratory study of respiratory function, people with MND had better-preserved lung capacity despite similar reductions in respiratory muscle strength compared to those with other NMDs, who were stiffer. People with MND reported fewer RTIs and while a lower VC and PCF were noted in people with a RTI, the sensitivity and specificity of these measures was not high.

These findings support the hypothesis that lung capacity is influenced by weakness initially, but that lack of flexibility of the lungs or chest wall may have a compounding effect.
Sheers N,1,2,3 Howard ME,1,2,3 Rochford P,1,3 Dirago R,1,4 Naughton P,1 Rigoni A,1 Berlowitz DJ,1,4

The physiological effects of a single session of lung volume recruitment in people with motor neurone disease

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Background

Lung volume recruitment (LVR) is a simple and inexpensive technique that uses a specially designed resuscitation bag to deliver deeper breaths. Using the bag to assist inspiration, consecutive inflations are delivered until maximal assisted lung insufflation capacity (LIC) is reached. At LIC, the lungs are near-fully inflated and chest wall expanded. Some guidelines advocate daily use, with the aim of maintaining respiratory “flexibility”, lung function and avoiding infections. Only one previous study has measured compliance (stiffness), a hypothesised mechanism behind these proposed benefits, hence study aims were to describe the short-term physiological effects of LVR on lung capacity, cough and total respiratory system compliance ($C_{rs}$).

Methods

Vital capacity (VC), peak cough flow (PCF), static lung volumes, $C_{rs}$, LIC and assisted PCF (PCF$_{LIC}$) were measured before (T0) and after (T2) a single session of LVR in community-dwelling participants with MND and respiratory system involvement. Ability to perform LVR was defined as LIC-VC difference >10% above VC.

Results

Twenty-five out of 27 people with MND were able to perform LVR. Lung volume recruitment increased volume during the manoeuvre (mean±SD VC$_{T0}$ 2.12±0.75 vs LIC$_{T0}$ 2.62±1.05 L) however we found no augmentation of cough flow (PCF$_{T0}$ 187±61 vs PCF$_{LIC,T0}$ 192±65 L/min). Respiratory system compliance improved following LVR therapy ($C_{rs,T0}$ 0.041±0.027 vs $C_{rs,T1}$ 0.050±0.027 L/cmH$_2$O). However there was no carry-over effect on volume or cough flow between T0 and T1 (VC$_{T0}$ 2.14±0.75 vs VC$_{T1}$ 2.09±0.77 L; PCF$_{T0}$ 185±61 vs PCF$_{T1}$ 191±66 L/min).

Discussion

A session of LVR improved $C_{rs}$ by an amount comparable to the only other study in people with MND that investigated physiological mechanisms, however in contrast we found no increase in cough flow or lung capacity before and after this single session. Longer-term treatment studies are necessary to determine how large any effect might be and whether it is sustained over time.
**Benefit versus Burden of Regular Respiratory Physiotherapy in Neuromuscular Disease: A Follow-up Questionnaire**

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**Aims:** Lung volume recruitment (LVR), and deep breathing exercises (DB) are simple and inexpensive respiratory therapies that may help people living with a neuromuscular disease (NMD). This study aimed to understand the perceived benefits and burden of these therapies and to investigate why participants continued therapy or not.

**Methods:** Participants involved in a randomised controlled trial (RCT) comparing LVR and DB were offered training in either therapy at completion. Twenty participants were contacted 6-12 months after RCT completion and consented to a telephone survey, comprising 20 open-ended, short-answer or 5-point Likert-scale questions, aiming to understand the experience, barriers and enablers of these therapies.

**Results:** Sixty-five percent (n=14) of participants continued with a respiratory therapy post trial. Participants in both groups identified the exercises as helpful (LVR 9, DB 7) and encouraged positive thoughts about their condition (LVR 9, DB 5). More participants performing LVR identified a greater change in cough strength (LVR 8, DB 3) and mucus clearance (LVR 6, DB 1) compared to DB.

Major barriers to performing regular respiratory therapy were having less energy or time because of the exercises, and dependency on others to complete (LVR). Four themes emerged from the open-ended questions: therapies made no change to their condition (LVR 2, DB 4), the need for more support with continuing therapy (LVR 2, DB 3), the need to understand the benefit of the therapy (LVR 2, DB 1) and the belief that their condition was too severe to be assisted by the therapies (BS 2, LVR 1).

**Conclusion:** Overall both the qualitative and the quantitative data suggests that whilst patients had positive experiences to performing LVR and DB, barriers existed. The results demonstrate the need for evidence-based information when commencing therapies, and ongoing support from therapists.
Measuring adherence to long-term assisted ventilation

Introduction:
Non-adherence to long-term assisted ventilation may risk persistent symptoms, unplanned hospitalisations or premature mortality for those that require this treatment. Previous studies have reported non-adherence rates of up to 50% but limited data are available from Australian populations.

Aim
The primary aim was to determine the usage of long-term assisted, non-invasive ventilation (NIV) during the initial six months of therapy in naive users. Secondary aims were to examine adherence patterns across demographics, disease groups and locations of care.

Methods
A prospective observational study was undertaken enrolling consecutive patients commencing NIV during an inpatient or outpatient visit to a centralised home mechanical ventilation service based in Victoria. Participant usage (minutes per day) was collected over their first six months after implementation of NIV via manual device downloads. Adherence per month of use was categorised as an average usage of greater than 4 hours per night.

Results
Data from 86 of the 100 participants enrolled was available for analysis. Missing data was primarily due to device malfunction or failure to attend for follow-up. The majority (65%) of participants had a diagnosis of motor neuron disease (MND), were implemented on NIV in an outpatient setting (72%) and lived in Melbourne (70%). Twenty two percent, all with MND, died within the study period. During the first month after NIV initiation, people with MND were significantly less likely to be able to adhere with NIV (27 of 56 (48%), versus 22/30 (73%), p=0.028). At study conclusion (6 months or the month prior to death in those with MND), overall adherence was 61%. Only a small number of those with MND shifted from non-adherent to adherent (n=3) during the observation period.

Conclusion
Non-adherence is common in those commencing NIV, especially in people with MND, despite enrolment within a centralised home mechanical ventilation service. Strategies aimed at reducing non-adherence rates may improve health outcomes.
Aim
Social support before and after childbirth is a possible protective factor for perinatal depression. It may also be a protective factor for adverse child development, which is a known consequence of perinatal depression. Previous studies of social support and perinatal depression have generally been short-term and cross-sectional. This study examined the trajectory of the relationships of perceived social support with depression and anxiety in pregnancy and postpartum as well as with child development and parenting-related stress up to 2 years.

Methods
The present study followed up a cohort from a randomised controlled trial of psychological treatment for antenatal depression (n=54). Perceived social support, depression and anxiety were assessed twice in pregnancy and twice postpartum up to 2 years using the Social Provisions Scale, Beck Depression Inventory and Beck Anxiety Inventory. Parenting-related stress was assessed at 24 months postpartum using the Parenting Stress Index. Child development was assessed at 9 months using the Revised Infant Behaviour Questionnaire Short Form, the Ages and Stages Questionnaire and the Ages and Stages: Social Emotional and at 24 months using the Bayley Scales of Infant Development and the Child Behaviour Checklist.

Results
There was a strong relationship between perinatal depression and anxiety and two aspects of social support, Reassurance of Worth and Reliable Alliance, particularly in late pregnancy and this was maintained to 6 months postpartum. Consistent with this finding, social support predicted the parent domain score of the Parenting Stress Index at 24 months. However, the effect of postnatal depression on child development at 9 and 24 months postpartum was not mediated by social support.

Conclusion
Social support may play a protective role against mood disorders in pregnancy. Given the deleterious effects of antenatal depression on maternal and child wellbeing, developing interventions that increase social support from late pregnancy may be especially important.
The Role of Glycolysis in Progression of Renal fibrosis

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Aim: Fatty acid oxidation is reduced in renal fibrosis but the role of glycolysis is unclear. We mutated a key controller of glycolysis in mice to determine its effect on renal fibrosis.

Methods: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB) is a key regulator of glycolysis. Mice with inactivating mutations of the phosphorylation sites in PFKFB2 (PFKFB2 KI mice) were generated, which is predicted to reduce the ability to increase the rate of glycolysis following stimulation. Unilateral ureteric obstruction (UUO) and folic acid nephropathy (FAN) models were used.

Results: In both UUO (p<0.01) and FAN (p<0.05) models, there was reduced expression of PFKFB2 in WT mice versus controls. In the UUO model, there were significant increases in fibrosis in PFKFB2 KI mice when assessed by picrosirius red staining (p<0.001), RT-PCR and Western blots for alpha-SMA (p<0.05) and fibronectin (p<0.05) compared to WT. Glycogen increased in both KI and WT mice following UUO, but lipid accumulation, measured by oil red O (p<0.005), was greater in PFKFB2 KI mice. In contrast, similar studies with the folic acid nephropathy (FAN) model showed no significant increase in fibrosis, greater glycogen content in the PFKFB2 KI mice compared to WT (p<0.05), and no difference in lipid accumulation.

Conclusions: These data show that inhibition of the regulation of glycolysis by PFKFB2 increases fibrosis in the UUO but not the FAN model.
Accurate measurements of dose calibrator gain settings with high purity germanium detector spectroscopy.

**Background:** Dose calibrators (DC) are operated as standard with manufacturer specified gain settings that have been shown to differ from those measured experimentally. Accurate determination of these settings is essential for dose optimisation in therapeutic and diagnostic applications.

**Aims:** This work presents a method of calibrating DC gain settings against a primary standard with quantitative high purity germanium (HPGe) detector spectroscopy for a range of nuclear medicine isotopes.

**Methods:** The efficiency of an HPGe detector was measured according to a primary standard and used as a ground truth to optimise a monte carlo model for efficiency calculations in the 88-1332 keV photopeak range. Modelled efficiencies of sources in extended geometries were validated with experimental measurements and used to cross calibrate DC gain settings against the primary standard. Gain settings for different models of DC were subsequently determined by comparison. The HPGe detector measured gain settings were cross checked against positron emission tomography measurements of standard uptake value (SUV) for applicable isotopes.

**Results:** The monte carlo model was optimised to produce efficiency values to within ±3.9% at 95% confidence. The discrepancies between activities measured with default gain settings and those measured with HPGe detector spectroscopy are shown in table 1. The HPGe detector measured gain settings agreed with SUV measurements to within 8.2%.

**Table 1:** Percentage difference in activity with default and HPGe detector measured gain settings.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Activity Difference %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-18</td>
<td>-1.0</td>
</tr>
<tr>
<td>Ga-68</td>
<td>0.8</td>
</tr>
<tr>
<td>Tc-99m</td>
<td>1.6</td>
</tr>
<tr>
<td>C-11</td>
<td>0.8</td>
</tr>
<tr>
<td>Zr-89</td>
<td>9.6</td>
</tr>
<tr>
<td>Cu-64</td>
<td>22.0</td>
</tr>
<tr>
<td>I-124</td>
<td>29.0</td>
</tr>
</tbody>
</table>

**Conclusion:** Using manufacturer specified gain settings resulted in erroneous activity measurements of high-energy beta emitters or isotopes with extraneous decay pathways. Accurate determination of DC gain settings is essential, particularly in light of high energy beta emitters such as Lu-177 becoming increasingly prevalent in therapy.
A high performance liquid chromatography quality control method for 4-[18F]Fluorobenzyl
dexetimide (4-[18F]FDEX)

Kenneth Young, Uwe Ackermann, Adam Livori, Amanda To, Victor L Villemange, Christopher C Rowe, J Gordon Chan

Molecular Imaging and Therapy, Austin Health, Melbourne

**Background / Aims:** 4-[18F]FDEX is a new radioligand for positron emission tomography (PET) imaging of muscarinic acetylcholine receptors (mACHR) particularly M1 subtype. This radioligand is promising diagnostic agent for cognitive dysfunction in schizophrenia.

Our department has developed and optimised the HPLC quality control method to evaluate the in-house radiosynthesis of 4-[18F]FDEX for human clinical trial.

**Method:** Phenomenex Luna 5µm C18 75 x 4.6mm column with 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) at a flow rate of 0.5 mL/min with a gradient from 5% (B) to 90% (B) in 16 minutes. Shimadzu HPLC system with FlowRam radioactive detector was used for UV absorbance and radioactive detection. LabSolution software from Shimadzu was used for analysis.

FDEX, flurobenzaldehyde (precursor 1) and nordexetimide (precursor 2) reference were prepared to determine the separation efficacy of our HPLC method. Serial dilution of each was also performed to determine the minimum detectable concentration and establishing standard a curve for specific activity calculation.

**Results:** Base line separation was achieved with retention times of flurobenzaldehyde, FDEX and nordexetimide were approximately 7, 11 and 14 minutes respectively. Standard curve of FDEX yielded a r² value of 1 with a minimum detectable limit of 1 µg/mL.

**Conclusion:** We have developed a robust HPLC method to evaluate the in-house production of 4-[18F]FDEX for human trial.
Ask an Informationist – engaging with the evidence

Issue:

The Choosing Wisely framework encourages clinicians and patients to ask questions and examine the evidence around the necessity of tests or treatment options. For clinicians today, the amount of information available can be overwhelming. Does emerging evidence question existing practices; or has a previous finding been overturned through new research? These key questions inform evidence-based practice decisions, enabling delivery of the most appropriate level of care.

Objectives:

*Ask an Informationist* is an initiative that translates clinical questions into practice. As a member of the Austin Health Choosing Wisely Steering Committee, the Austin Health Sciences Library brings expertise in evidence-based literature searching. A clinical question, directly related to the evidence for tests, treatments or procedures, is submitted to the Steering Committee. The Library team create an infographic as a visual summary of the available evidence, supported by a written report. When coupled with audit data or local policies and procedures, this provides an evidence-rich foundation for clinicians to initiate change and “Choose Wisely” in their delivery of patient care.

Outcomes and impact:

To date, six infographics and reports have been produced: intravenous magnesium in atrial fibrillation; continuous intravenous PPIs for acute non-variceal upper gastrointestinal bleed; minimum retesting intervals in microbiology tests; the necessity of opioids for pain management following limb fracture; the management of renal colic; and the use of pregabalin in acute neuropathic pain.

The impact of *Ask an Informationist* is seen throughout Austin Health. The initiative has: driven change in emergency department practice for intravenous magnesium use; led to delivery of clinical education around PPIs through workshops and media activities; been a catalyst for broader discussion around opioid use throughout the hospital.

Through this collaboration we are engaging with the evidence, encouraging critical thinking and shaping the future of our patient care.

Michele Gaca – Austin Health Sciences Library
Helen Baxter – Austin Health Sciences Library
Clinical utility of next generation sequencing in AML: a real-world experience

**Aim:** Acute myeloid leukaemia (AML) is a genomically heterogenous disease [1, 2]. Advanced molecular techniques, principally next generation sequencing (NGS), are required to analyse the multiple genes of diagnostic, prognostic and therapeutic relevance [3]; yet NGS is relatively expensive, poorly reimbursed and requires expertise for implementation and interpretation [4, 5], resulting in variable access to this technology. The clinical utility of NGS testing in routine care of Australian AML patients is unknown. This study evaluates the impact of NGS in AML management in an Australian tertiary hospital.

**Methods:** Patients (n=45) were retrospectively identified; comprehensive clinical and pathological data was collected from medical records. Clinical utility was defined by a change in diagnosis (WHO classification), prognosis (ELN risk stratification; predicted three-year overall survival calculated by an online multistage prediction tool) and/or therapy (CR1 allograft recommendation; targeted therapy) following addition of NGS results to standard diagnostics.

**Results:** NGS was clinically significant in more than one third of patients (16/45). In the newly diagnosed cohort (n=40), NGS led to changes in WHO diagnosis (1 patient), ELN risk stratification (7 patients), >10% change in predicted overall survival (11 patients) and change to allograft recommendation in first complete remission (2 patients), primarily through the detection of RUNX1, ASXL1 and TP53 mutations in baseline ELN intermediate risk disease. Of particular note is the 39% of patients (7/18) upgraded from intermediate to adverse risk by detection of these mutations. 3 patients received targeted therapy after NGS; one with a novel FLT3 mutation received midostaurin, and 40% of relapsed patients (2/5) received IDH1/2 inhibitors.

![Figure 1: Impact of NGS analysis on ELN risk categorisation](image)

**Conclusion:** NGS testing is clinically useful in a significant proportion of AML patients, particularly those with ELN intermediate risk and relapsed disease. Funding for NGS as a standard-of-care investigation for AML should be strongly considered; further data supporting the clinical utility of NGS will lend weight to this argument.

**References:**
Aim
Refractory fevers in haematology patients with prolonged and severe neutropenia raises suspicion for invasive fungal infection (IFI). This study aimed to estimate the prevalence of pulmonary IFI in high-risk haematology patients on antifungal prophylaxis, and analyse the outcomes of routine chest CT and its impact on the evaluation and management refractory febrile neutropenia (FN) in this cohort.

Methods
A retrospective analysis of haematology inpatients with refractory FN investigated with chest CT whilst on antifungal prophylaxis between 2010 and 2018 was conducted. Patient demographic and clinical information regarding FN characteristics and chest CT outcomes was analysed with descriptive statistics. The primary endpoint was the proportion of FN episodes in which chest CT led to a diagnosis of probable or proven pulmonary IFI. Secondary endpoints included the proportion of chest CT scans that led to bronchoscopy and bronchoalveolar lavage (BAL)/lung biopsy or a change in antifungal/antibacterial therapy, as well as the presence of respiratory symptoms/signs, positive smoking status, and positive blood cultures.

Results
140 eligible FN episodes were identified. Overall, 6 cases (4.29%) were identified to have probable or proven pulmonary IFI, of which 4 (2.86%) were invasive pulmonary aspergillosis (IPA); 100% of these cases exhibited respiratory symptoms/signs, and 83.33% had a positive smoking history. Importantly, 67.14% of the chest CT scans did not result in a change in management, and 82.35% of the bronchoscopy and BAL procedures performed due to chest CT yielded no significant results.

Conclusion
The prevalence of pulmonary IFI in this sample group of high-risk haematology patients on antifungal prophylaxis was quite low (<5%), and our findings suggest that routine chest CT in the evaluation of refractory FN in this cohort may lead to excessive investigation. These observations provide the rationale for future larger cohort studies to further investigate clinical features (i.e. respiratory symptoms/signs and smoking status) and risk factors for breakthrough pulmonary fungal disease that could facilitate the more directed (rather than routine) use of chest CT in this setting.
Measurable residual disease detection by next generation sequencing in B-cell acute lymphoblastic leukaemia

1. Clinical Haematology, Austin Health, Melbourne Australia
2. Molecular Diagnostics, Austin Pathology, Melbourne Australia

Introduction
Measurable residual disease (MRD), a key prognostic factor in B-cell acute lymphoblastic leukaemia (B-ALL), is traditionally assessed by flow cytometry and/or allele specific oligonucleotide PCR (ASO-PCR). Here we use novel next generation sequencing (NGS) technology to measure MRD. Our aims are to determine the sensitivity of a NGS based assay for MRD and define normalisation techniques for result standardisation.

Methods
Bone marrow samples were analysed using the LymphoTrack® Dx Assay Panel to detect IgH gene rearrangements. The IgH locus was amplified using primers targeted at three conserved framework (FR1-3) regions of the variable gene segments and corresponding joining gene segments. Target genes were sequenced on the Illumina® MiSeq with data analysis undertaken using provided software. Sequence clonality determination was defined as >2.5% of the total reads and >2x the read frequency for the third most frequent sequence. Clinically relevant MRD timepoints were analysed as above in 3 replicates. A 100 cell equivalent spike-in control (LymphoQuant™) was added in each MRD replicate for normalisation. Serial dilution of a commercially obtained known IgH rearrangement was performed to determine the limit of detection of the assay.

Results
Results were concordant (82.86%) between assay methods with the exception of 6 samples. In 5 cases MRD was detected by NGS at a lower level than flow cytometry and ASO-PCR which were negative. MRD positivity by NGS corresponded with poor clinical outcomes in these patients. The dilution series validates the ability of the assay to detect 1 leukaemic cell in 100,000 normal cells (10^{-5} sensitivity). Replicates of diagnostic samples within and across sequencing runs demonstrate the intra/inter run precision of the assay.

Conclusion
MRD detection by NGS is complementary to standard of care testing using flow cytometry and ASO-PCR. NGS has the added advantage of increased sensitivity, detection of clonal evolution and a rapid turnaround time. Normalisation of MRD levels to cell equivalents is required to suitably compare results with flow cytometry and ASO-PCR.
Bethany Palmer¹, Robert Millar¹,², Amelia Chiappazzo¹

Do parents make good decisions when bringing their child to the Emergency Department? Comparing GP and parent-referred paediatric emergency presentations.

1. University of Melbourne, Parkville, Victoria
2. Austin Hospital, Melbourne, Victoria

Aim
To determine whether the demographics and outcomes of parent-referred paediatric emergency presentations significantly differ from GP-referred presentations.

Methods
A cross-sectional prospective study, conducted from January to May (2019), in the Paediatric ED at Austin Hospital in Melbourne, Australia. Study sample was all paediatric presentations of all triage categories aged 15 or under. Measured outcomes were demographic data (age, sex, triage category and arrival mode) and outcome data (admission, specialty consultation, consultation time greater than 1 hour, intravenous/ nasogastric therapy, procedural sedation, procedures, imaging studies and pathology collection).

Results
The demographics of parent-referred presentations were not significantly different to GP-referred patients but were more likely to arrive via ambulance (13% vs. 2%, p<0.01). GP-referred patients triaged to category 4 and 5 (low-urgency) were more likely to require a procedure (risk difference 0.07, 95% CI 0.02 - 0.13) and pathology (risk difference 0.05, 95% CI 0.01 - 0.1) than parent-referred presentations. The proportion of low-urgency presentations who required no measured outcomes was not significant between the two referral sources (risk difference -0.02, 95% CI -0.07 - 0.03). Current policy to decrease ED overcrowding suggests diverting low-urgency emergency presentations to GPs(1). Objective results demonstrate that parents and GPs are making similar referral decisions.

Conclusions
The demographics and outcomes of parent-referred paediatric emergency presentations do not substantially differ from GP-referred presentations. Policy focused on diverting low-urgency cases to GPs is likely to be ineffective.

References
Kelsey Hibberd and Ian Baldwin

*Austin Health. Dept of Intensive Care and Clinical Education Unit.*

**Nursing handover tools in the ICU ; A practice survey.**

**Background.**

Nursing handover in the Intensive Care Unit (ICU) is bedside and commonly between two nurses for the introduction, background, current status, plan of care, and transfer of responsibility to the next shift.

At Austin Health we use a dedicated and designed A5 page two sided document for short notes and prompts associated with handover. This includes a job list to time brackets, assessments, and any follow up. Some of these notes are used for the next handover, and as a reminder when completing clinical notes and check off requirements for care standards and safety.

**Aims.** To investigate the use of any similar document in ICU’s across Australia and International.

**Methods.** Telephone contact was made to 15 hospitals using a prepared question algorithm to ask: If any document was used? If Yes; was the document purpose designed and the basic elements? If no, what is used at nursing handover for this purpose?

**Results.** 15 or 100 % of those interviewed indicated no formal document was available and nurses referred to history and admission notes and clinical notes made on paperer charts and or computer screen views. 10 or 75% indicated scrap paper and or clinical progress documents were used, and later discarded; i.e. scrap paper again.

All reflected this is a need, and they would appreciate the opportunity to see the Austin ICU version and idea.

**Discussion.** There is a need to provide a paper document with basic structural headings as a tool for personal and reminder notes to link the complex clinical data and presentations of such in multiple Software views at a bedside in the ICU.

**Conclusion.** We believe our existing tool is clearly unique, has originality and could progress better method and structure for handover and nursing work in the ICU.
Patients With Diabetes Are At No Greater Risk For Contrast Induced Nephropathy Than Those Without Diabetes

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1. Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia. 2. Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia. 3. The Florey Institute of Neuroscience & Mental Health, Melbourne, Victoria, Australia. 4. Department of Administrative Informatics, Austin Health, Heidelberg, Victoria, Australia. 5. Department of Radiology, Austin Health, Heidelberg, Victoria, Australia. 6. Department of Endocrinology, and Diabetes, St Vincent’s Hospital Melbourne, Melbourne, Victoria, Australia

Background

- Contrast-induced nephropathy (CIN) is an important cause of kidney injury in inpatients.
- Prevalence and predisposing factors of CIN as a result of iodinated intravenous (IV) contrast are unclear in diabetes. Limited studies have examined the association of CIN and diabetes.
- Incidence of CIN is variable between 3 to 30%, depending on pre-existing co-morbidities. Risk increases if patients have underlying renal disease and/or diabetes1,2.

Objectives

1. To investigate the association between CIN and Diabetes Status.
2. To investigate the potential modifying effect of Diabetes on the association between baseline creatinine and CIN.

Methodology

- As part of the Austin Health Diabetes Discovery Initiative, routine HbA1c testing was performed on all inpatients aged ≥54 years if no HbA1c was available within the preceding 90 days.
- Routine HbA1c results were extracted from the hospital electronic system, Cerner Millennium IT Health Platform3.
- Inpatients who received IV contrast prior to computed tomography (CT) scans from July 2012 to March 2018 at Austin Health, Melbourne were identified.
- Serum creatinine measurements at baseline, 48 hours and 72 hours post contrast administration were obtained.
- CIN was defined as:
  - an absolute rise in serum creatinine of ≥44 μmol/L from baseline after 48 and/or 72 hours or
  - a relative measurement of ≥25% increase from baseline after 48 and/or 72 hours.

Patients were divided into those with or without a history of diabetes and/or diabetes.

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetes (n=441)</th>
<th>No Diabetes (n=990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 (64-78)</td>
<td>72 (63-86)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.7 (5.9-7.7)</td>
<td>5.4 (5.4)</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>14.9 (8-21)</td>
<td>13.0 (8-20)</td>
</tr>
<tr>
<td>Charlson score†</td>
<td>3.2 (2.5)</td>
<td>1.0 (2.3)</td>
</tr>
<tr>
<td>Baseline Creatinine</td>
<td>94 (71-135)</td>
<td>75 (63-91)</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>75 (53-91)</td>
<td>94 (71-135)</td>
</tr>
</tbody>
</table>

* Charlson comorbidity index - a validated method of weighting chronic medical conditions (the score for diabetes and age were excluded as they were analysed as a separate variable).

Table 2: Prevalence of CIN

<table>
<thead>
<tr>
<th></th>
<th>CIN Calculated with Absolute Method</th>
<th>CIN Calculated with Relative Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48 Hours</td>
<td>72 Hours</td>
</tr>
<tr>
<td></td>
<td>Overall Prevalence</td>
<td>Overall Prevalence</td>
</tr>
<tr>
<td></td>
<td>5.4%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>No Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>No Diabetes</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>3.9%</td>
</tr>
<tr>
<td>No Diabetes</td>
<td>6.4%</td>
<td></td>
</tr>
</tbody>
</table>

- Overall, for every baseline creatinine increments of 10 μmol/L, the chance of developing CIN was 5% higher measured using absolute method at 48 or 72 hours.
- After adjusting for baseline creatinine and age, there was no difference in the prevalence of CIN between patients with and without diabetes.

Conclusion

- Patients with or without diabetes who had a CT scan with IV contrast appear to have a similar risk for the development of CIN after adjusting for other variables.
- Patients with higher baseline creatinine had a higher risk of developing CIN.
- A larger data set may yield different outcomes.

Acknowledgements

Diabetes Discovery Initiative Team, Department of Endocrinology, Department of Radiology, The Florey Institute of Neuroscience and Mental Health, Austin Centre for Applied Clinical Informatics, Department of Administrative Informatics, Department of Pathology, Department of Medicine, University of Melbourne – Austin Health, Department of Endocrinology and Diabetes, St Vincent’s Hospital Melbourne.

References

1. Lower EE et al. Radiology 1997;203:605-10
Moore N, Detering K, Low T, Nolte L, Fraser S, Sellars M

Doctors’ perspectives on adhering to advance care directives when making medical decisions for patients: an Australian interview study

Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Australia; Advance Care Planning Australia, Austin Health, Melbourne, Australia; Clinical Gerontology Division, National Ageing Research Institute, Parkville, Victoria, Australia; Kolling Institute, Northern Clinical School, Faculty of Medicine, University of Sydney, Sydney, Australia

Background
Advance care planning (ACP) assists people to identify their goals, values and treatment preferences for future care. Ideally, preferences are documented in an advance care directive (ACD), to be used by doctors to guide medical decision-making should patients subsequently lose their decision-making capacity. However, studies demonstrate that ACDs are not always adhered to by doctors in clinical practice.

Aim
To describe the attitudes and perspectives of doctors regarding ACD adherence and the utility of ACDs in clinical practice.

Methods
Doctors from a variety of medical specialties and with varying experience levels were recruited from a large tertiary hospital in Melbourne, Australia. Face-to-face semi-structured interviews were conducted using three case-based vignettes to explore doctors’ decision-making and attitudes towards ACDs. Transcripts were analysed using thematic analysis.

Results
Twenty-one doctors were interviewed, 48% female (10/21). Most (19/21) reported having experience using ACDs. Four themes were identified: aligning with patient preferences (avoiding unwanted care, prioritising autonomy, navigating family opposition), advocating best interests (defining futile care, relying on clinical judgement, rejecting unreasonable decisions, disregarding legal consequences), establishing validity (doubting rigor of the decision-making process, questioning patients’ ability to understand treatment decisions, distrusting outdated preferences, seeking confirmation) and translating written preferences into practice (contextualising patient preferences, applying subjective terminology, prioritising emergency medical treatment).

Conclusion
ACDs provide doctors with opportunities to align patient preferences with treatment and uphold patient autonomy. However, doctors experience decisional conflict when attempting to adhere to ACDs in practice, especially when they believe that adhering to the ACD is not in the patients’ best interests, or if they have doubts about the validity of the ACD. Future ACP programs should consider approaches to improve the validity and applicability of ACDs. In addition, there is a need for ethical and legal education to support doctors’ knowledge and confidence in ACP and enacting ACDs.
Are we overdosing older people with paracetamol in hospital?

Olivia Reid,1 Samanta Lalic,2,3 Rohan Elliott1,3

1. Pharmacy Department, Austin Health; 2. Medicines Optimisation Service, Austin Health; 3. Centre for Medicine Use and Safety, Monash University

Background
Paracetamol can cause hepatic injury when used in excessive doses. Older people may be at increased risk. Some guidelines recommend a maximum paracetamol dose of 60 mg/kg/day for older people who weigh < 50kg, especially in the presence of frailty or chronic disease.1,2

Aim
To determine whether older hospital inpatients weighing < 50kg are prescribed potentially excessive paracetamol doses.

Method
Patients aged ≥70 years at a large metropolitan teaching hospital admitted between August and December 2018, with length-of-stay >72 hours, weight < 50kg and prescribed paracetamol were included in this retrospective audit. Medication data, including the total dose of paracetamol administered on the first full day after paracetamol was prescribed, and the dose prescribed on discharge, were extracted from patients’ electronic medical records. The primary endpoint was the percentage of patients who received a potentially excessive paracetamol dose (>60 mg/kg/day).

Results
One hundred and eight older patients who weighed < 50kg (mean age 85.6 years, 90.7% female) received paracetamol during 120 hospital admissions. They received an average of 10.1 medicines, indicating a high level of multimorbidity. During 63/120 (52.5%) admissions, patients received >60 mg/kg/day of paracetamol (mean dose 81.3 mg/kg/day, range 61.2-117.3). On 72 occasions, patients were prescribed paracetamol on discharge, and 61 (84.7%) of these were >60 mg/kg/day (mean dose 87.0 mg/kg/day, range 61.2-129.0). Most inpatient and discharge paracetamol orders were for regular administration (84.2% and 65.2% respectively).

Conclusion
More than 50% of hospital inpatients aged ≥70 years who weighed < 50kg received potentially excessive doses of paracetamol. Strategies are required to raise awareness of the need to reduce paracetamol doses in older patients who weigh < 50kg.

References
Reduced handgrip strength in liver transplant recipients is associated with poor outcomes after transplantation

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2University of Melbourne, School of Medicine, Dentistry and Health Sciences.
3Department of Surgery, Austin Health, Melbourne
4Liver Transplant Unit, Austin Health, Melbourne

Aim:
Sarcopenia and frailty are common in patients with liver disease. Handgrip strength (HGS) has recently been shown to predict wait-list mortality in liver transplant (LT) candidates but little is known about its association with post-transplant outcomes. This study aimed to evaluate the impact of reduced HGS on a range of clinical outcomes after LT.

Methods:
This is a retrospective review of all adult patients undergoing LT between January 2009 and December 2016. Functional muscle strength was assessed by HGS at wait listing and repeated prior to LT. Study outcomes included length of stay (LOS) in ICU and hospital, episodes of infection, rejection and biliary strictures within 90 days, readmission within 90 days, and graft and patient survival.

Results:
373 patients (70% male, median age 55 years [IQR 47; 60], MELD 13 [9; 19]) were included. 175 patients (47%) had impaired HGS at time of LT wait listing, with mean HGS 32.4kg (±9.32) for males and 18.4kg (±6.29) for females. There was a small but significant decline in muscle strength following median waiting time of 142 days [52; 318] to 31.4kg (±9.35) for men (p=0.006) and 17.6kg (±5.78) for women (p=0.037).

Impaired HGS at LT was associated with significantly longer ICU LOS (82 hr vs 63 hr, p=0.032), increased hospital LOS (21 d vs 15 d, p<0.001) and increased incidence of infection (48% vs 33%, p=0.003) compared to those with adequate HGS. Logistic regression showed the lowest quartile of gender-specific HGS independently predicted adverse post-LT outcomes, including: longer ICU LOS (HR 0.69 [0.54; 0.88], p=0.003), longer hospital LOS (HR 0.73 [0.58; 0.93], p=0.011), and development of infection (OR 1.83 [1.12; 2.97], p=0.015). There was no significant association between HGS and prevalence of rejection, biliary complications, hospital readmission, graft loss or survival.

Conclusion:
Low HGS is common in patients awaiting LT and we report for the first time its association with adverse clinical outcome after transplantation. HGS offers a simple, objective, repeatable measure of muscle function that allows clinicians to identify LT candidates at risk of early post-transplant morbidity.
Authors: Riddiough GE\textsuperscript{1,2}, Tran BM\textsuperscript{2}, Fifis T\textsuperscript{1}, Walsh K\textsuperscript{1}, Kastrappis G\textsuperscript{1}, Muralidharan V\textsuperscript{1}, Perini MV\textsuperscript{1}, Vincan E\textsuperscript{2,3}, Christophi C\textsuperscript{1}

Title: Recurrence of colorectal liver metastases in the regenerating liver

Affiliations: \textsuperscript{1}Department of Surgery, University of Melbourne, Austin Health, Lance Townsend Building, Level 8, 145 Studley Road, Heidelberg, VIC, 308. \textsuperscript{2}The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Parkville, VIC, 3010. \textsuperscript{3}Victorian Infectious Diseases Reference Laboratory, The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Parkville, Victoria, 3010

Acknowledgements: University of Melbourne RTP Scholarship, Reg Worcester Foundation for Surgery Scholarship, Royal Australasian College of Surgeons

Background and Aim
Emerging clinical and experimental data suggests that processes which stimulate liver regeneration post hepatectomy also drive tumour recurrence and that biochemical events occurring in the tumour periphery and tissue adjacent to the tumour appear to be key to this. This is a major problem for hepatobiliary surgeons and oncologists. We investigated the mechanisms underlying CRLM recurrence in the regenerating liver and the efficacy of treatment with renin-angiotensin inhibitors (RASi) to attenuate this.

Methods
All animal experiments were approved by the Austin health animal ethics committee. Liver metastases were established using mouse colorectal cancer (MoCR) cells routinely passaged subcutaneously in CBA mice and induced via splenic injection. One week later, 70\% partial hepatectomy (PH) or sham surgery was performed. Mice received either captopril (renin-angiotensin inhibitor) or saline. Mice were culled at day 16 and livers were collected for tumour burden calculations, QRT-PCR and immunohistochemistry. Human CRLM samples were obtained from consenting adults, with approval of the Austin Health human ethics committee and used to culture patient-derived organoids. These are currently being optimised.

Results
PH stimulates tumour growth (p=0.04*) and is associated with significantly higher Ki67 staining in both the tumour and liver (p=0.04* and p<0.01* respectively). PH also upregulated markers of epithelial-to-mesenchymal transition (EMT), such as vimentin and Zeb-1 in the tumour (p=0.04* and p=0.01* respectively). Inhibition of the renin-angiotensin system was associated with a significant reduction in tumour burden post hepatectomy (p=0.04*). Preliminary data from our human samples indicate that tissue from the tumour periphery/adjacent tissue region more consistently generates tumour organoids.

Conclusion
PH stimulates CRLM progression in the regenerating liver and this effect can be attenuated by administering RASi. One mechanism for tumour progression in the regenerating liver appears to be upregulation of EMT and this may explain why organoids grown from the adjacent tumour regions develop better.
“First do no harm”: significance of delays to surgery in patients with non-metastatic breast cancer.
Xu, J., Bromley, L., Chew, G., Yeo, B.
University of Melbourne, Austin Health, Olivia John Cancer Research Institute.

Aim/Background
The majority of patients in Australia with non-metastatic breast cancer will undergo primary surgery with curative intent. This involves many complex decisions that inevitably increase time from diagnosis to surgery. Current guidelines suggest surgery should occur within 30 days of a decision to treat. However, there may be appropriate reasons to justify a delay to surgery. This study aims to analyse factors that contribute to an increased time to surgery (TTS) and establish whether the associated wait time is justifiable in the context of improved individualised breast cancer management.

Methods
This is a retrospective analysis of all patients at Austin Health surgically managed for non-metastatic invasive breast carcinoma between 2013 and 2019. TTS was defined as time between informed diagnosis and cancer surgery. Patients were categorised into TTS groups of ≤30 and >30 days. Kaplan-Meier survival analysis was used to evaluate the impact of TTS on survival outcomes.

Results
A total of 842 patients were included. Median number of days to surgery was 34 days. 43.9% of the total cohort received surgery within the recommended 30 days. Factors identified to be associated with an increased TTS were screening, transfer of care, ER positive tumour, mastectomy, immediate reconstruction and use of pre-operative imaging including MRI and staging scans. Median follow up for the cohort was 30 months. Between wait groups of ≤30 and >30 days, there were no significant association found between TTS and survival outcomes for DFS (HR 1.20 95% CI 0.56 to 2.60) and OS (HR 1.58 95% CI 0.82 to 3.03).

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>MEDIAN DAYS TO SURGERY</th>
<th>ODDS RATIO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened vs. symptomatic</td>
<td>35 vs. 27</td>
<td>2.39 (1.77 to 3.23)</td>
</tr>
<tr>
<td>Transfer of care vs. none</td>
<td>35 vs. 27</td>
<td>2.31 (1.73 to 3.10)</td>
</tr>
<tr>
<td>Mastectomy vs. BCS</td>
<td>34 vs. 28</td>
<td>1.78 (1.31 to 2.43)</td>
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<tr>
<td>Immediate reconstruction vs. not</td>
<td>36 vs. 29</td>
<td>2.32 (1.55 to 3.48)</td>
</tr>
<tr>
<td>ER positive vs. ER negative</td>
<td>33 vs. 28</td>
<td>2.05 (1.34 to 3.14)</td>
</tr>
<tr>
<td>Pre-operative MRI scan vs. none</td>
<td>35 vs. 29</td>
<td>2.07 (1.36 to 3.24)</td>
</tr>
<tr>
<td>Pre-operative staging vs. none</td>
<td>34 vs. 28</td>
<td>1.58 (1.18 to 2.12)</td>
</tr>
</tbody>
</table>

Table 1. Factors associated with a significant increase in time to surgery

Conclusions
Breast cancer management involves many complex factors that significantly increases time from diagnosis to surgery. Surgery within 30 days of diagnosis is not associated with improved DFS and OS. Time delays associated with integral element of care should be used to guide a revision of current TTS recommendations.
Evaluation of the practice of intravenous to oral antimicrobial switch in hospitalised patients.

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Aim
Early switch from intravenous (IV) to oral antimicrobials (IV-to-oral switch) is a key antimicrobial stewardship strategy to optimise antimicrobial prescribing. A guideline incorporating criteria to determine patient eligibility for IV-to-oral switch and recommended oral alternatives was implemented at Austin Health in 2017. We aim to explore concordance with the guideline.

Method
A retrospective review of general medicine and surgical patients admitted to wards 7E, 7W, 8E & 8W and prescribed ≥ 1 IV antimicrobial(s) for ≥ 48 hours, over a 2-month period (29 Oct to 21 Dec, 2018), was undertaken. Data collected included variables in the IV-to-oral switch criteria, infection type, microbiology results, antimicrobials prescribed and total duration of IV and oral therapy. The appropriateness of IV-to-oral switch, including choice and dose of oral alternative(s), was assessed by an infectious diseases pharmacist and physician.

Results
One-hundred and seven IV antimicrobial patients/courses were evaluated. Intra-abdominal (30.9%), lower respiratory tract (27.4%), urinary tract (19.4%) and skin and soft tissue (11.5%) infections were the most common reasons for antimicrobial prescription. IV antimicrobials prescribed were mainly ceftriaxone (31.1%), amoxicillin-clavulanate (19.3%), benzylpenicillin (9.6%), metronidazole (8.1%) and cefazolin (8.1%). Forty-six (43%) patients did not switch within 24 hours of meeting criteria. The median total duration (days) of IV therapy before a switch was made was 3 (interquartile range 2.25 to 5). In 20 patients (18.7%), the choice/dose of the oral alternative was considered inappropriate. Approximately 50% of patients received antimicrobial therapy exceeding the recommended duration of therapy for the infection by one or more days.

Conclusion
Overall the practice of IV-to-oral switch at Austin Health was generally concordant with the guideline. Whilst 43% of patients did not switch when the criteria was met, the median number of days before switch was short. Prolonged duration of therapy was identified as a target for improving antimicrobial prescribing.
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Therapeutic potential of targeting the protective arm of the renin angiotensin system in cirrhotic and non-cirrhotic portal hypertension

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Introduction

Portal hypertension (PHT) and bleeding from varices is the major cause of morbidity and mortality in patients with cirrhosis. Splanchnic vasodilatation which leads to an elevated portal venous inflow plays an important role in the pathogenesis of PHT. This study investigates the role of vasodilatory Mas and Mas-related G-protein coupled receptor type D (MrgD) in PHT and whether blockade of these receptors produce a clinically significant reduction in portal pressure (PP) in cirrhotic and non-cirrhotic animals with PHT.

Methods

Cirrhotic PHT was inducted in Sprague-Dawley rats by bile duct ligation (BDL) surgery or twice-weekly carbon-tetrachloride (CCl₄) injections. Non-cirrhotic PHT was inducted by partial portal vein ligation (PPVL) surgery. Two-weeks (BDL), 8-weeks (CCl₄), and 1-week (PPVL) after each procedure, rats received either MasR blocker A779 or MrgD blocker D-Pro⁷-Ang-(1-7) (D-Pro) (28µg/kg/hr) via subcutaneously implanted osmotic mini-pumps. Saline infused sham-operated or diseased rats served as controls. After treatment, rats were cannulated to measure PP. Coloured microsphere injections were used to calculate splanchnic vascular resistance (SPVR) and mesenteric blood flow (MBF). Mesenteric resistance vessels isolated from separate groups of CCl₄ rats were used in myographs to study their vasodilatory properties.

Results

D-Pro and A779 significantly (p<0.01) reduced PP in BDL and CCl₄ rats compared to saline-infused controls. In CCl₄ rats PP reduction from the baseline was larger with D-Pro (33%) than A779 (21%). Treatment with both drugs increased SPVR, however, in CCl₄ model, this was greater with D-Pro than that of A779, leading to a marked reduction in MBF (by >50%). D-Pro but not A779 profoundly reduced vascular relaxation of first order (45%) and 2ⁿᵈ/3ⁿᵈ order (13%) vessels in response to acetylcholine. In contrast, neither D-Pro nor A779 had any effect on SPVR, MBF or PP in non-cirrhotic PPVL rats.

Conclusion

These findings demonstrate profound effects of blockade of newly identified receptor, MrgD, on PP in cirrhotic but not in non-cirrhotic PHT. MrgD but not MasR blockade showed splanchnic vasculature-specific effects in cirrhosis. We therefore conclude that MrgD, is a potential target for the design of drugs that can specifically block splanchnic vasodilatation in cirrhotic PHT, and we have commenced work to develop small molecule MrgD blockers.