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Early High Flow Nasal Cannula Therapy in Bronchiolitis, a prospective randomised control trial: A Paediatric Acute Respiratory Intervention Study (PARIS)

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Introduction. Bronchiolitis imposes the largest health care burden on non-elective paediatric hospital admissions worldwide, with up to 17 % of cases requiring admission to intensive care. The early use of non-invasive respiratory support devices in less intensive scenarios to facilitate earlier respiratory support may have an impact on outcome by avoiding progression of the disease process. High Flow Nasal Cannula (HFNC) therapy has emerged as a new method to provide a non-invasive form of positive pressure support. There is a lack of high-grade evidence on use of HFNC therapy in bronchiolitis.

Methods. Prospective multi-centre randomised trial comparing standard treatment and High Flow Nasal Cannula therapy in infants with bronchiolitis admitted to 17 hospitals emergency departments and paediatric wards in Australia and New Zealand, including 12 non-tertiary regional/metropolitan and 5 tertiary centres (NHMRC funded project 2015-2017). The primary outcome is treatment failure; defined as meeting three out of four pre-specified failure criteria requiring escalation of treatment or higher level of care. Secondary outcomes include transfer to a tertiary institution, intensive care admission, length of stay, length of oxygen-treatment, intubation, need for non-invasive/invasive ventilation, and cost.

Results. Results by September 2015 include: Screening of >5300 patients and enrolment of 650 patients across 17 centres in Australia and NZ. No adverse events occurred to date. The proposed protocol has been adapted and implemented across 17 regional, metropolitan and tertiary centres.

Conclusions. The current high enrolment rate anticipates that the trial will prematurely be finalised following winter 2016, with results pending early 2017.

Paper to Practice. This study will improve our understanding of oxygen therapy in bronchiolitis infants. These findings will be adapted to standardised clinical practice guidelines across Australia and NZ.

2

The WAU(weighted activity unit)effect: evaluating the cost of DRG (diagnosis related group) coding

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Introduction. Queensland Hospital budgets are set using an Activity Based Funding(ABF) model and WAU's(Weight Activity Units) per price approach. ABF funding relies on Diagnosis Related Group(DRG) classifications of hospital encounters by Hospital Coders, who match specific terms documented in medical charts. Each principle DRG has allocated WAU values. We explored any cost consequences when charts were reviewed by an oncology registrar, familiar with the nuances of note documentation.

Methods. Medical oncology admissions from 1st January to 30th June 2014 were identified and the actual DRG coding obtained from Hospital Coders. Charts were reviewed by a medical oncology registrar for diagnoses additions/changes. Coders then evaluated for principle DRG and WAU value variance. Total cost consequences were calculated by applying 1 WAU=$4676 (as per Queensland 2014).

Results. 109 encounters were initially identified for 72 patients. 7 further encounters were incidentally discovered (patient transferred to medical oncology from another team). 95/116(81%) had additional diagnoses captured, leading to a DRG and WAU change in 26 encounters. The total reimbursement variance was $143404.07. Chart documentation issues included use of abbreviations unable to be coded, non-continuous notes scattered in different sections of the chart, and diagnoses not written despite treatment delivered as per medication charts.

Conclusions. Admission/discharge notes are often written by the most junior staff. Ultimately the information entered determines future funding in our healthcare system.

Paper to Practice. Improvements in documentation are needed to reflect the dynamic care received and attract appropriate funding reimbursement.

3

The prevalence and clinical impact of common pathogens isolated from adolescents and adults with cystic fibrosis, 2001-2014.

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Background: Currently there are a growing number of adults with cystic fibrosis (CF) and airway infection plays a significant role in their health outcomes. Aggressive antibiotic treatment aimed at eradiating early *P. aeruginosa* infection is now commonly administered throughout paediatric CF care centres.

Objectives: Therefore we sought to determine if changing patterns of care and treatment are impacting on the airway microbiology of adults with CF, with a focus on those transitioning from paediatric care.

Methods: A comprehensive analysis of sputum microbiology results was undertaken on all patients attending the Adult CF Centre (ACFC) at The Prince Charles Hospital between 2001 and 2014. The clinical status and health outcomes of patients at time of transition from paediatric care were assessed.

Results: A significant decrease in the prevalence of *P. aeruginosa*, MRSA, *B. cepacia* complex and *A. fumigatus* ($p=0.001$, $p<0.001$, $p=0.002$ and $p<0.001$, respectively) was seen during the study. Rates of chronic *P. aeruginosa* infections was stable ($p=0.25$). Current infection, at time of transition from paediatric care, with *P. aeruginosa* or *B. cepacia* complex, was associated with increased lung transplantation and increased rates of death. There was a strong association between a decline in the prevalence of *P. aeruginosa* and increasing lung function over time for the paediatric cohort.

Conclusion: A significant decrease in prevalence has been reported for many of the major CF airway pathogens within this cohort. Of note is the decline in prevalence of *P. aeruginosa* seen within the paediatric patients at time of transition. This result is associated with an increase in lung function. Ongoing analysis of airway microbiology and health status of paediatric patients will be vital in determining the long term impact of aggressive antibiotic treatment in early life.

Paper to Practice: Respiratory infections are a leading contributor to death in people with CF, therefore monitoring the trends of airway pathogens is vital. Using a surveillance tool we clearly demonstrate the success of infection control and patient segregation that is implemented at the ACFC.

4

A pilot study of early discharge in delirium; A light on the hill?

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Background Hospital length of stay in delirium is frequently prolonged. The ideal of reorientation within the unfamiliar environment of a hospital is a challenge. Therefore, a supported early discharge scheme for patients with a diagnosis of delirium was developed and evaluated.
Methods A prospective intervention (Hospital in the Home: HITH) versus historical control (standard care) methodology was used for patients with a diagnosis of delirium. Patients who were >65 years and who were admitted to the internal medicine services at The Prince Charles Hospital (TPCH) with a Confusion Assessment Method (CAM) diagnosis of delirium and a full-time carer at home, were eligible for an early discharge scheme with HITH services . The HITH intervention comprised an individualized, multidisciplinary and multifaceted management program. Patients were discharged from HITH once delirium free for 48 hours according to daily CAM scoring.
Results Sixteen patients with a diagnosis of delirium were discharged on the early discharge scheme. Mean age was 84.9 years and median clinical frailty scale was 7. Average length of acute in-hospital stay was reduced by 17 days compared with usual care (p=0.02). Combined rates of readmission and mortality were 31% versus 27%, respectively; p=0.7. The new model of care was associated with an estimated total saving of $313,600. All caregiver responses (13/16) recommended the service to prospective users.
Conclusions There is scope for an early discharge model of care in delirium.
Paper to Practice The HITH delirium pathway provides an alternative discharge model for elderly, frail patients suffering from delirium. Patients are discharged from hospital earlier and their risk of developing hospital related complications is reduced. Patients receive timely, consistent multidisciplinary care in their own homes and ongoing care needs are also addressed.

5

Verbal communication in tracheostomised mechanically ventilated patients leads to improved respiratory mechanics

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Verbal communication in tracheostomised mechanically ventilated patients leads to improved respiratory mechanics.

Introduction. Due to voicelessness, communication is often a source of frustration for tracheostomised mechanically ventilated patients. Speaking valve (SV) is a one-way valve used to enable verbal communication. Recently, data was reported that with SV in-situ end-expiratory lung volumes (EELV) increased. However, there are no published data on ventilation distribution or the potential effect of SV on the diaphragm – an important muscle for breathing. This study aimed to assess EELV distribution and abdominal to chest ratio when using SVs with these ICU patients.

Methods. Twenty consecutive tracheostomised ICU patients weaning off mechanical ventilation and using an in-line SV were recruited. Ten patients were receiving Pressure Support Ventilation and 10 were on High Flow Oxygen. All patients were monitored using Electrical Impedance Tomography and Respiratory Inductance Plethysmography pre, during and post 30min of SV use. Outcome measures included EELV distribution and abdo:chest ratio.

Results. The patients showed increased EELV with a significant increase ($p<0.001$) in all regions of the lungs during 30min with SV in ventilation circuit. EELV continued to increase in all regions post SV removal ($p<0.001$). This increase happened irrespective of the patients' ventilation status. There was a significant increase in abdo:chest ratio ($p=0.03$) indicating increased abdominal mobility suggestive of improved diaphragm activity with SV.

Conclusions. SV use in this cohort of mechanically ventilated patients resulted in likely improved recruitment of the patients' lungs with increased diaphragm activity. More research is needed to determine whether this could lead to shorter ventilator weaning times, and improved ICU outcomes.

Paper to practice. By demonstrating that SVs are safe and beneficial to ICU patients' that still require mechanical ventilation has lead to wide use of SVs, with 75% of tracheostomised patients having a voice throughout most of their ICU stay.

6

Improved Bone Mineral Density Observed in Ivacaftor Dosing Patients with Cystic Fibrosis (CF) and a G551D mutation

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Introduction: Low bone mineral density (BMD) is common in people with CF. CFTR is thought to have a direct role in bone development and metabolism. Ivacaftor is the first licensed, oral systemic CFTR potentiator therapy and results in substantial improvements in pulmonary and nutritional health in CF patients who carry at least one G551D *CFTR* gene mutation. However, the effect of Ivacaftor on bone strength has not previously been reported.

Methods: A retrospective review of BMD results and other proven clinical indicators of response to Ivacaftor in the longer term dosing patients was undertaken.

Results: Serial (pre and post dosing) BMD investigations of the L2-L4 lumbar spine (LS) and the femoral neck (FN) has been performed in six dosing patients. At commencement of Ivacaftor, the median (IQR) age, BMI and FEV_1 of the group were: 29.3 (22 – 38) years, 19.4 (17.9 – 20.9) kg/m^2 and 54.0 (36.3 – 65.4) % predicted. Post-dosing BMD measurement was performed at 490 ± 328 days (mean ± SD) after commencement of Ivacaftor. A mean (SD) increase in BMD of 5.4% (3.8) for the LS and 1.9% (1.3) for FN was observed in the group. The LS BMD improvement in four of the 6 patients was considered significant. A positive correlation in sweat chloride reduction and increased spine BMD was found (r=0.86, p=0.021).

Conclusions: Improved LS BMD in patients on Ivacaftor for more than 2 years has been observed. It is unknown whether the increased BMD results from a primary effect of Ivacaftor on CFTR function within bone or secondary to improvements in general health (e.g. improved nutrition / exercise). To address this question, analysis of the effects of Ivacaftor therapy on bone turnover is ongoing.

Paper to Practice: This is the first time that BMD changes have been reported in patients dosing with Ivacaftor has been reported.

7

Reducing Readmissions within Internal Medicine Services – The Patients' Perspective

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Introduction: The frequency of hospital re-admissions for patients to acute wards has been observed to be increasing in recent times. Risk of re-admission has previously been shown to be reduced by ensuring active patient involvement in discharge planning which also improves patient satisfaction with services.
Methods: A prospective cross-sectional study using qualitative methods was conducted. Participants were patients who had been re-admitted to hospital within 28 days of discharge. Structured interviews were conducted in person during their hospital re-admission where possible, or by telephone post-discharge if required.
Results: Thirty participants were interviewed with 26 completed in person. The majority of participants (70%) reported their current admission related directly to their previous admission and 40% felt re-admission could have been avoided. Participants indicated their re-admission related to: an unresolved or recurrent acute medical issue, readiness for discharge, reduced adherence to the discharge care plan, and lack of general practitioner (GP) involvement post-discharge. Participants perceived post-discharge recovery may have benefited from a key person co-ordinating their discharge plan (73%), with a post-discharge phone call from this person (77%), and being provided their discharge care plan (63%).
Conclusions: The majority of participants perceived that their re-admission to hospital was related to their previous admission and a large number felt it could have been avoided with small changes in practice. In keeping with previous literature recurrent or unresolved medical issues played a significant role in hospital re-admission, but through simple pre- and post-discharge system and process changes that actively involve the patient's transition home could be improved and potentially re-admissions prevented.
Paper to Practice: Through understanding the patient perspective of the discharge planning, process systems can be improved with a view to reducing hospital re-admission rates.

8

Visual analogue symptom score predicts length of stay in acute exacerbations of chronic airways disease

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Background: The relationship between symptom severity and the aetiology of exacerbation in airway diseases such as asthma, COPD and non-CF bronchiectasis is not clear. Similarly, a comparison of symptom severity in these diseases has not been undertaken during exacerbations and an investigation of how improvements in symptom scores may correlate with objective improvements in indices such as lung function has not been performed.

Aim: We developed a visual analogue score (VAS) encompassing cough, breathlessness, sputum purulence and volume and general well-being and used it to assess patient symptom severity and inflammatory phenotype during a hospital admission for treatment of a pulmonary exacerbation of asthma, COPD and NCFB.

Methods: Patients with Asthma, Chronic obstructive pulmonary disease (COPD) and non-CF bronchiectasis (NCFB) presenting to the Prince Charles Hospital with an acute exacerbations (AE) were recruited. Nasopharyngeal swab for viruses were performed, Symptom specific questionnaires were completed, blood samples were assessed for inflammatory markers and immunophenotyping of peripheral blood mononuclear cells.

Results: 27 patients admitted with an acute exacerbation of chronic lung disease were enrolled (11 asthma, 13COPD, 10 NCFB). Patients reported cough (r=0.41, P0.009), Sputum volume (r=0.47, P=0.003) and purulence (r=0.45, P=0.007) and Appetite (r=0.37, P=0.019) and total symptom score (r=0.46, P=0.003) on admission were each significantly associated with increased length of stay. Reported symptoms were similar between viral and bacterial induced exacerbations.

Conclusion: Subjective reported symptoms of admission predict length of stay, but do not differentiate between viral and bacterial precipitants. Correlation of symptoms with detailed immunophenotype is ongoing.

Paper to Practice: Determination of a clinico-immunological fingerprint which accurately identifies virus induced AE will allow the development of a point-of-care test which will rapidly identify patient in need of respiratory isolation.

9

It was a swell journey: partnering with consumers and community service providers to develop consumer centred Lymphoedema clinical pathways.

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Introduction. There is strong evidence that having consumers actively participate in service improvement initiatives can significantly benefit clinical outcomes and experience of care. The MNHHS Lymphoedema Working Party recently invited consumers to actively participate in a two year service redesign project. The project aimed at improving access to Lymphoedema services for patients. A number of ministerial complaints had been raised by consumers due to limited access to local services.
Methods. A multidisciplinary working party undertook extensive service analyses and consultation with consumers, GPs, non-government organisations, private providers and MNHHS multidisciplinary teams to determine bottlenecks and barriers in the system, existing service capacity and opportunities for improved access. Solutions to these barriers were explored in close collaboration with consumers and other stakeholders. Consultation was achieved via written surveys and a number of face to face forums.
Results. With only one dedicated Lymphoedema Service based at RBWH it was not surprising that approximately 70% of patients who received care actually lived closer to another MNHHS hospital. Access was also limited in the not for profit and private sectors. Evidence based, multi-sector and multidisciplinary clinical pathways which utilise and maximise resources in existing community-based services were developed. These are currently being trialled at Redcliffe Hospital. The pathway will be supported by a 'Map of Medicine for Lymphoedema' (in development) and contemporary app based consumer resources (in development).
Conclusion. Involving consumers has lead not only to increased consumer satisfaction in MNHHS (with two good news stories published in the local papers) but has resulted in the development of consumer centred, evidence based clinical pathways.
Paper to Practice. This experience and learnings from the different methods of consumer consultations can be replicated and shared widely across any number of clinical projects.

10

Transfusion-Related Immune Modulation: Impact of Dose and Ex-vivo Storage of Platelet Concentrates on Dendritic Cell Responses

Ms Alexis Perros[1,2,3], Ms Anne-Marie Christensen[3,4], Professor Robert Flower[3,4], Dr Melinda Dean[1,3,4]
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Introduction. Platelet concentrates (PC) are used to treat thrombocytopenia and trauma, and in Australia, have a shelf-life of 5 days, with an extended shelf-life of 7 days under consideration by the TGA. During storage, biological and biophysical changes occur, referred to as the "storage lesion". Mechanisms underlying recipient immune responses following PC transfusion, including transfusion-related immunomodulation (TRIM), remain largely unknown. This studied investigated the immunomodulatory capacity of PC on dendritic cells (DC), a key immune mediator, using an *in-vitro* whole blood transfusion model.

Methods. PC-supernatants (PC-SN) collected from PC stored for 2, 5 and 7 days were cultured with "recipient" whole blood and RPMI at a dose corresponding to a 1, and, 2-3 unit transfusion. Lipopolysaccharide (LPS, 1µg/mL) was added in parallel to model infection. DC inflammatory responses were measured intracellularly using flow cytometry.

Results. Exposure to PC-SN alone, regardless of dose or length of storage, had minimal impact on DC inflammatory responses. In the presence of LPS, PC-SN exposure suppressed DC IL-10, IL-8, IL-6, IL-12, MIP-1β, IL-1α and TNF-α production in a dose-associated manner ($P<0.05$).

Conclusions. Using an *in-vitro* blood transfusion model, these novel findings suggest that soluble mediators present in clinical PC suppress DC function, particularly in a model of infection. Importantly, PC dose, more than storage, had a profound impact on DC inflammatory responses.

Paper to Practice. Given the central role of DC in the immune response, these findings suggest DC modulation may contribute to transfusion-related complications in some patients. Importantly, this study provides clear evidence of dose-associated suppression of DC function, suggesting larger dose of PC transfusions may increase transfusion-associated complications (e.g. TRIM). This study also suggests that extended 7 day PC storage would not adversely impact DC mediated responses.

11

Hydrodynamic Evaluation of Aortic Cardiopulmonary Bypass Cannulae Using Particle Image Velocimetry

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Introduction. Cardiopulmonary bypass (CPB) is required for mechanical circulatory support during several cardiac procedures. The CPB arterial cannula is inserted into the distal ascending aorta, while its design and placement in an atherosclerotic aorta can contribute to neurologic deficits post-cardiac surgery, with stroke and other cognitive deficits occurring in up to 30% of patients after surgery. The aim of this study was to analyse the exit jet profile and velocities in various dispersion and non-dispersion cannulae to provide guidance for clinical selection to reduce neurological deficits.

Methods. Particle image velocimetry was used to assess 19 (7 dispersion and 12 non-dispersion) adult arterial CPB cannulae in a clear Perspex chamber using a rotary blood pump. Pump speed was set to deliver flow rates of 3 and 5 L/min with each cannula. The fluid (water/glycerol at 60/40% by mass) was seeded with particles, which were tracked using 20 image pairs under continuous flow conditions. The maximum velocity of the exit jet was assessed at 20 and 40 mm from the cannula tip at both flow rates with each cannula.

Results. Dispersion and non-dispersion cannulae were characterized by a fan shape and narrow velocity profile respectively. With the exception of one cannula, all dispersion cannulae had lower maximum velocities than non-dispersion cannulae. Of the 19 cannulae, the respective highest and lowest velocities at 20 mm from the tip were 3.06 (non-dispersion) and 0.63 m/s (dispersion) at 5 L/min and 1.55 (non-dispersion) and 0.25 (dispersion) at 3 L/min.

Conclusions. Due to lower exit velocities and subsequent jet forces on the aortic wall, dispersion cannulae may cause less damage to tissue and might preferentially be selected for atherosclerotic aortas.

Paper to Practice. This study may assist the surgeon in choosing the best cannula for each patient and operation type based on the cannula hydrodynamic performance.

12

Acute exacerbations of COPD are associated with a distinct MAIT and regulatory T-lymphocyte profiles

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Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with significant morbidity and mortality. Differentiating between viral or bacterial triggers is important to guide therapy and infection control policies. Current viral and bacterial identification methods are relatively slow and we therefore hypothesised that T cell immune signatures would be more informative and potentially provide a rapid point of care test.

Aim: Determine whether patients suffering an AECOPD demonstrate distinct immunophenotypes and whether, immune profiles can be used to differentiate between viral and bacterial exacerbations and predict response to therapy

Methods: In a pilot study, peripheral blood mononuclear cells were isolated from 11 patients admitted to hospital with an AECOPD. Nine age-matched healthy subjects provided control data. Detailed Immunopheotyping was performed with a focus on the presence and activation status of regulatory T-lymphocytes (Treg) and Mucosal associated invariant T-lymphocytes (MAIT) cells.

Results: The peripheral blood of patients admitted with an AECOPD contained an increased proportion of Treg cells compared to healthy controls (5.1% v's 2.5%, p=0.006). Compared to healthy controls an increased proportion of Tregs from patients with AECOPD expressed the activation marker CD69 (72% v's 53.8%, P=0.028) and decreased expression of the inhibitory receptor PD-1 (7.3% v' 17.3%, P=0.002). MAIT cell proportions were not significantly different between healthy controls and AECOPD, however, MAIT Cells from AECOPD demonstrated distinct activation patterns, with decreased expression of CTLA-4 (30.4% v's 98.7%, P<0.001) and PD-1 (51.5% v's 98.7%, P<0.001). Furthermore MAIT cells from patients with AECOPD and a positive viral swab less frequently expressed the regulatory protein TIM-3, than patients with positive sputum bacterial cultures.

Conclusion: patients undergoing pulmonary exacerbations of COPD demonstrate distinct MAIT and Treg activation profiles compared to healthy controls. Ongoing longitudinal analysis is proceeding to determine whether immunophenotyping can distinguish between viral and bacterial induced AECOPD to direct and predict response to treatment.

Project to practice: Identification of an immunophenotype that differentiates viral from bacterial induced AECOPD may allow the development of a point-of-care test that can be used to direct targeted treatment.

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A novel in vitro evaluation strategy for the successful clinical translation of bone substitute materials

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Osteoblast lineage cells are direct effector cells for osteogenesis and, therefore, commonly used to evaluate the *in vitro* osteogenic capacity of bone biomaterials. This strategy has achieved certain success when developing novel bone biomaterials; however, inconsistent results between *in vitro* and *in vivo* studies are not uncommon. Some candidate bone biomaterials developed applying this strategy are later found to perform below expectations *in vivo* without satisfying new bone regeneration, suggesting the mechanisms that govern the material's capacity to mediate osteogenesis requires further investigation. The emerging field of osteoimmunology and immunomodulation in osteogenesis has informed a paradigm shift in our view of bone biomaterials–from one of an inert to an immune-osteomodulatory material–highlighting the importance of immune cells in the material-mediating osteogenesis. Neglecting the importance of the immune response during this process may be a major shortcoming in the current assessment and could explain the inconsistence between *in vitro* and *in vivo* conditions. In this study we evaluated a potential angiogenic bone substitute material cobalt incorporated β-tricalcium phosphate (CCP) using both a traditional and a novel approach to assess osteogenesis, the latter including the use of immune cells. It was found that CCP extract by itself was sufficient to enhance osteogenic differentiation of bone marrow stem cells (BMSCs), whereas this effect was attenuated when macrophages were involved. In response to CCP, macrophages switched M1 phenotype extreme, releasing pro-inflammatory cytokines and bone destructive factors. When the CCP materials were implanted into a rat femur condyle defect model, there was an increase of inflammatory markers and bone destruction, coupled with fibrous encapsulation rather than new bone formation. These findings demonstrated that the inclusion of immune cells in the *in vitro* assessment matched the *in vivo* tissue response, and provides a more accurate indication of the essential role of immune cells when assessing material-stimulated osteogenesis *in vitro*.

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A potential indirect pathogenic role for Prevotella in the CF respiratory microbiota

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Introduction. *Prevotella* species are the dominant obligate anaerobes in the CF respiratory microbiota. We found that *Prevotella* isolates exhibit ceftazidime resistance associated with extended-spectrum β-lactamase (ESβL) production. The study aim was to ascertain if an ESβL-positive *Prevotella* isolate could protect *Pseudomonas aeruginosa* from the action of ceftazidime (passive resistance).

Methods. Time-kill studies were carried out (*Prevotella* monoculture; *P. aeruginosa* monoculture; co-culture) using ceftazidime at a concentration of 64X (32 mg/mL) the *P. aeruginosa* MIC. A protective effect by *Prevotella* was defined as a ≥2 $\log_{10}$ increase in viable count of *P. aeruginosa* at 48 hours compared with that of *P. aeruginosa* alone. The viable count of *P. aeruginosa* in the presence of ceftazidime +/- *Prevotella* was compared using a paired samples t-test.

Results. At 48 hours the difference in *P. aeruginosa* viable count between the co-culture (1.63×10^6 CFU/mL) and monoculture ($<2 \times 10^2$ CFU/mL) was >2 $\log_{10}$ CFU/mL indicating a protective effect by the ESβL-positive *Prevotella* isolate. The difference in total viable count of *P. aeruginosa* at this time-point was statistically greater when cultured with compared to without the *Prevotella* isolate ($P = 0.03$).

Conclusions. Our study supports the hypothesis that β-lactamase-producing *Prevotella* species shield *P. aeruginosa* from treatment with ceftazidime potentially contributing to the persistence of lung infection with this pathogen.

Paper to Practice. When deciding on appropriate treatment for polymicrobial infections, β-lactamase production by all bacteria belonging to the microbiota may need to be considered.

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Pulmonary Valve Opening When Using Dual Left-Rotary Blood Pumps for Bi-Ventricular Support

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Introduction. Rotary blood pumps (RBPs) are mechanical devices that usually support the left ventricle (left-RBP). Right ventricular failure is a common complication associated with left-rotary blood pump support (RBP). As no long-term right-RBP exists, clinicians have implanted left-RBPs to support the right-side. To meet lower pulmonary pressures, right-RBPs must be operated with reduced speed, or with a banded outflow graft. These modes differ in hydraulic performance, which may influence pulmonary valve opening (PVO) morphology. Permanent valve closure is detrimental to patients as it may lead to commissural fusion, valve insufficiency and thrombus formation. This study aimed to compare PVO with a right-RBP in reduced speed and outflow banding. We also assessed the effect of a pump speed management system (PSMS), which automatically adjusts pump speeds to match cardiac demand, on PVO.

Methods. Normal, hypo- and hyper-tensive patients with severe bi-ventricular failure were simulated in-vitro using a mock circulation loop. Cardiac output was restored to 5.0 L/min for each simulated patient condition with banding, reduced speed and PSMS modes. SVR and PVR were systematically changed until PVO was identified or ventricular suction occurred.

Results. Banding the right-RBP outflow increased the PVR range (≤450 dyne.s.cm^{-5}) while maintaining PVO in all tests. SVR ranges with PVO were highest with the PSMS (≤2400 dyne.s.cm^{-5}), which eliminated ventricular suction, followed by outflow banding (≤2100 dyne.s.cm^{-5}). The reduced speed mode resulted in the smallest range of SVR and PVR with PVO in all conditions.

Conclusions. Right-RBP outflow banding allowed for PVO over greater range of PVR and SVR in comparison to the reduced speed mode. The addition of PSMS further increased the ranges of SVR.

Paper to Practice. Clinicians should consider banding the outflow instead of reducing the right-RBP speed to allow PVO in order to reduce the risk of commissural fusion, insufficiency and thrombus.

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Intratumoural genomic heterogeneity in never smokers' primary lung adenocarcinoma

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Introduction. Lung cancer is a leading cause of morbidity and mortality. Spatial and temporal genomic heterogeneity may provide insight into the mutagenic mechanisms. We sought to document the patterns of intratumoural heterogeneity in primary lung adenocarcinoma (LUAC) from never-smokers using whole genome sequencing (WGS).

Methods. WGS was performed on histologically confirmed LUAC from 8 never smokers (<100 cigarettes in a lifetime). DNA was kit extracted from samples that met pre-specified quality criteria prior to WGS on Illumina's HiSeq 2000 platform to minimum coverage of 80x, 40x and 30x for tumour, non-tumour lung and blood samples, respectively. Three cases underwent multi-region sequencing (2-4 regions per case). Data analysis was performed on an in-house pipeline. Copy number variant (CNV) calling was performed using Illumina's HumanOmni2.5-8 array data.

Results. A median 9907 (range 5936 – 31760) single nucleotide variants (SNVs)/small indels were detected per tumour region. Tumour regions were more similar genetically to other tumour regions from the same case than to different cases. 31% - 55% SNVs/small indels were common among all tumour regions for cases analysed by multi-region sequencing. Cases 2 and 3 demonstrated most high priority variants, those predicted to be likely to have functional significance, were common among all regions from a single case (Figure 1).

Conclusions. Intertumoural heterogeneity accounted for more genomic variation in LUAC from never smokers than intratumoural heterogeneity. A variable proportion of total SNVs/small indels, and a larger proportion of high priority variants, was shared among tumour regions taken from a single case.

Figure 1. Heat map of high priority single nucleotide variants detected by multiregion whole genome sequencing.

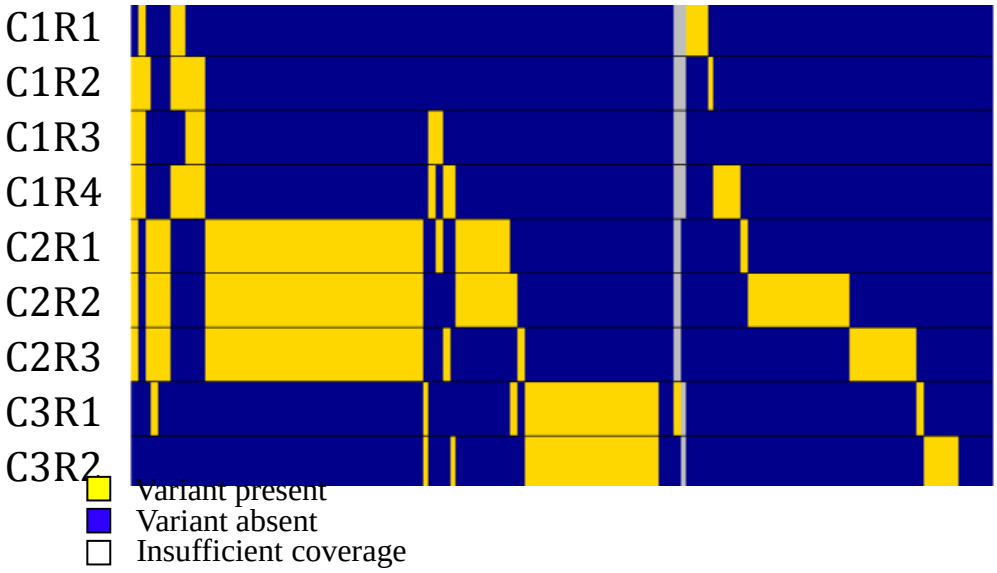

Figure 1 depicts variants detected by whole genome sequencing. Cases and tumour regions are listed on the left; C1 R1 refers to tumour region 1 of case 1. Three cases were analysed using multiregion sequencing; 4 regions are available for case 1, 3 for case 2 and 2 for case 3. Variants are depicted as vertical bars listed from left to right across the image. Yellow bars indicate the variant was detected, blue that the variant was absent and while bars indicate that there were fewer than 10 reads available at that locus in that tumour region and therefore a call was not made.

Paper to Practice.

This research highlights the genomic differences within lung tumours and raises questions for scientific and clinical communities. For example, diagnostic strategies commonly used to detect lung cancer rely on small biopsies. Spatial heterogeneity, such as that demonstrated in this paper, may cause sampling bias when looking for targetable mutations in small specimens. Ongoing studies of this phenomenon will quantify the risk, and ensure diagnostic strategies are safe and accurate.

In addition, lung cancer is usually not diagnosed at an early enough stage to offer curative treatment. Therapies only temporarily slow tumour growth, but may not work at all. An understanding of the processes driving tumorigenesis and its response to treatment, which leave footprints on the genome of a tumour, is an important step in ultimately deciphering and preventing, the fundamental cause of lung cancer.

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3D spheroids from mesothelioma cell lines at UQTRC (TPCH)

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Introduction. Three-dimensional (3D) tumour spheroid cultures mimic the microstructure of living tumours, retaining many characteristics important for the study of tumour behaviour and responses. We generated and evaluated the growth and characteristics of spheroids from four human mesothelioma cell lines (MM05, MM12, MM1081, MM1171).
Methods. Cells initially propagated as plastic adherent monolayers were seeded at 3500, 6500 and 10,000 cells per well, in supplemented RPMI 1640 culture medium using three different spheroid generation methods - overlay culture, hanging drop, and magnetic bioprinting. The morphology, size, and geometry of mesothelioma tumour spheroids were assessed visually and measured using imaging analysis software (ImageJ). Spheroid viability was assessed using PrestoBlue®, CellTiter-Glo®, and CellTox™ Green assays. Results were analysed using GraphPad Prism® 6.
Results. Spheroids were successfully generated in all culture conditions from all four lines. Spheroids from each line displayed similar characteristics irrespective of method. MM05 and MM12 spheroids were compact while MM1081 and MM1171 were loose cellular aggregates. A distinct growth pattern was observed for all cell lines – initially spheroid diameter reduced, then subsequently expanded. Viability assays reflected observed morphology for those lines that formed single spheroids (MM05, MM1081 and MM1171). MM12 formed a cluster of small spheroids initially that eventually aggregated into a single spheroid. PrestoBlue® and CellTox™ Green assay signals may reflect poor reagent penetration in larger spheroids.
Conclusions. We have shown that human mesothelioma cell lines can be propagated as spheroids in standard medium for several days. Improved method of evaluating spheroid viability is warranted.
Paper to Practice. These spheroids represent an in vitro model that preserves important tumour microstructure and may be suited to personalised predictive drug and molecular interference testing for patients.

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Neutrophil and monocyte inflammatory responses may contribute to the development of transfusion-related acute lung injury (TRALI)

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Introduction. Blood transfusion is a life-saving treatment; however, it is associated with fatal risks such as transfusion-related acute lung injury (TRALI). A two-insult mechanism has been hypothesised: the first insult being the patient's co-morbidity and inflammatory state, and the second insult being transfusion that exacerbates the patient's inflammatory state and precipitates TRALI development. Causative blood product factors include: (i) antibodies targeting class I or class II human leucocyte antigens (HLA) or human neutrophil antigens (HNA); and/or (ii) biological response modifiers (BRM) that accumulate in blood products during routine storage. Activation of neutrophils and monocytes has been implicated in TRALI pathogenesis; however, the precise underlying mechanisms remain uncertain.

Methods. Neutrophil-specific, monocyte-specific and overall inflammatory responses to potential causative factors for TRALI were measured using an *in vitro* transfusion model and flow cytometry. A monoclonal antibody (targeting HLA-II), a protein BRM (soluble CD40 ligand; sCD40L) and a lipid BRM (12-hydroxyeicosatetraenoic acid (HETE)) were used in the model, with or without lipopolysaccharide (LPS) to model underlying patient factors.

Results. Without LPS, inflammatory responses were suppressed following exposure to anti-HLA-II, sCD40L and 12-HETE, suggesting that in less ill patients, transfusion of blood products containing these factors may increase the risk of infection. In contrast, in an induced inflammatory state (i.e. with LPS), the addition of 12-HETE and/or anti-HLA-II resulted in pro-inflammatory changes, suggesting that in severely ill patients transfusion of blood products containing these factors may contribute to the development of TRALI. Thus, in both cases, the patient's risk of morbidity and mortality may be increased by transfusion.

Conclusions. *In vitro* models provide a useful tool to understand the mechanisms underpinning blood transfusion complications.

Paper to Practice. This study improved our understanding of TRALI pathogenesis and may contribute to identifying potential strategies to reduce the risk of TRALI and improve blood transfusion safety.