RESEARCH FORUM - 2021

Wednesday June 23, 2021
9:00-13:00

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Division of Respirology
Department of Medicine
Faculty of Medicine

Contact info:
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PROGRAM - RESPIROLOGY RESEARCH FORUM 2021 - June 23, 2021

8.30 Virtual coffee

9.00 Opening of the Respirology Research: Gaspard Montandon.

9.05 Director of the Division of Respirology – Dr. Douglas Bradley.

9.10 KEY-NOTE SPEAKER. Dr. Samira Mubareka, Assistant Professor. Sunnybrook Health Science Centre, University of Toronto.

From zoonotic origins to clinical challenges; perspectives on SARS-CoV-2

9.55 SESSION 1


10.05 Gabriel Burke. Patients are the people who teach me the most” – Exploring resident perspectives on the development of physician-patient communication skills (abstract #5).

10.15 Xiaoshu Cao. Association of obstructive sleep apnea with thoracic fluid volume and small airways narrowing in asthma during sleep (abstract #7).

10.25 Jean-Philippe Rousseau. Optogenetic activation of preBötzinger Complex cells alleviates respiratory depression by opioids (abstract #43).


10.45 BREAK

11.00. KEY-NOTE SPEAKER: Dr. Atul Malhotra, Professor of Medicine. University of California – San Diego.

UCSD Contributions to War on the COVID-19 Pandemic
11.45 SESSION 2

11.45 Nicole C. Kraus. Sex differential in survival: does it exist in a Canadian cystic fibrosis cohort.
11.55 Jan Lim. Assessing Obstructive Sleep Apnea Severity Through Application of Upper Airway Negative Pressure During Wakefulness.
12.05 Rayoun Ramendra. Donor airway bile acid as a biomarker of aspiration and predictor of post-transplant outcomes.

12.35 Awards of the Division of Respirology.

Password: 2021

Zoom link:
Topic: Respirology Research Forum
Time: Jun 23, 2021 08:30 AM Eastern Time (US and Canada)
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Organizers: Dr. Gaspard Montandon  Ms. Rhiannon Davies.  Ms. Andreea Furdui
Judges: Dr. Dmitry Rozenberg  Dr. Jean-Phillipe Rousseau  Dr. Ted Marras  Dr. Tereza Martinu
**KEY-NOTE SPEAKERS**

**Dr. Samira Mubareka**, Assistant Professor. Sunnybrook Health Science Centre, University of Toronto.

**From zoonotic origins to clinical challenges; perspectives on SARS-CoV-2**

Dr. Mubareka is a Clinician-Scientist at Sunnybrook Research Institute, a microbiologist, and an Assistant Professor in the Laboratory Medicine and Pathobiology - University of Toronto. In the early days of the COVID-19 pandemic, Dr. Mubareka and colleagues isolated the SARS-CoV-2 virus in a Level 3 containment facility. It is now the principal source of SARS-CoV-2 to most academic CL3 laboratories across the country.

Dr. Mubareka serves on the Chief Science Advisor of Canada’s COVID-19 Expert Panel, the Implementation Committee of the Canadian COVID-19 Genomics Network (CanCOGeN) Viral Sequencing Project (Genome Canada) and the Ontario Genomics’ Steering Committee for the Ontario COVID-19 Genomics Rapid Response Coalition. She has collaborated extensively with fluid dynamics engineers and others to fill gaps in the understanding of viral bioaerosol dispersion. In 2020, Dr. Mubareka formed the Sunnybrook Translational Research Program for Emerging and Respiratory Viruses (SERV) to focus on viral genomics, transmission and the development of medical countermeasures.
Dr. Atul Malhotra. Professor of Medicine. University of California - San Diego.

UCSD Contributions to War on the COVID-19 Pandemic

Dr. Malhotra is pulmonologist, intensivist, and research chief of Pulmonary, Critical Care and Sleep Medicine. He is active clinically in pulmonary, critical care and sleep medicine. In the sleep clinic, Dr. Malhotra provides a full spectrum of diagnostic and therapeutic services to patients with sleep-related disorders, including sleep apnea, insomnia, restless leg syndrome, narcolepsy and sleep disorders associated with medical or psychiatric conditions. He has a special interest in the treatment of sleep apnea.

As a professor in the Department of Medicine, Dr. Malhotra is involved in training medical students, residents and fellows at UC San Diego School of Medicine.

Dr. Malhotra was the recent president of the American Thoracic Society (2015-2016). He has taught and presented his research on sleep-related disorders locally, regionally, nationally and internationally. He has published more than 310 original manuscripts in leading journals plus 220 reviews and chapters. He is a principal- and co-investigator on numerous National Institutes of Health (NIH) grants relating to sleep apnea and serves as an ad hoc reviewer for many leading journals including the New England Journal of Medicine, Mayo Clinic Proceedings, Sleep and the Journal of American Medical Association. To view a full list of his publications, visit PubMed. He is an internationally recognized expert in sleep apnea.
1. **Ghadah Alrehaili.** The impact of lumacaftor-ivacaftor on health outcomes in Canadians with cystic fibrosis.


4. **Alina Blazer.** Excess healthcare utilization and mortality in younger adults with COPD.


7. **Xiaoshu Cao.** Association of obstructive sleep apnea with thoracic fluid volume and small airways narrowing in asthma during sleep.

8. **Eric Carelli.** Mortality and Cardiovascular Hospitalizations in Hemodialysis Patients with Sleep Apnea.

9. **Karan Chohan.** Assessment of Cardiac Autonomic Dysfunction in Chronic Thromboembolic Pulmonary Hypertension

10. **Adele Coriati.** International comparison of survival in Cystic Fibrosis between Canada, France and Australia.

11. **Adele Coriati.** The Impact of the High Emergency Lung Transplantation program in Cystic Fibrosis in France: insight from a comparison with Canada.

12. **Nermin Diab.** Long-term impact of COPD on postoperative cardiorespiratory morbidity and mortality: a population cohort study.

13. **Allen Duong.** Donor neutrophils and B cells in EVLP perfusate are associated with severe primary graft dysfunction.

14. **Brett Edwards.** Time to positive culture detection as a predictor of Mycobacterium avium pulmonary disease severity.

15. **Juan Fernandez.** Association between Esophageal Dysmotility and Long-term Outcomes in Lung Transplant Recipients.

16. **Manoela Ferreira.** How Ultrasound Can Predict Sarcopenia in Lung Transplant Candidates

17. **Lee Fidler.** Ophthalmologic assessments in patients with newly diagnosed sarcoidosis: an observational study from a universal healthcare system.

18. **Andreea Furdui.** The Role of Somatostatin-Expressing Cells in Opioid-Induced Respiratory Depression.


21. **Annie Jiang.** Lung Function in COVID-19 Intensive Care Unit (ICU) Survivors Assessed with Respiratory Oscillometry (Osc) and Conventional Pulmonary Function Tests (cPFT).

22. **Christopher Kawala.** Real-world use of ivacaftor in Canada: A retrospective analysis using the Canadian Cystic Fibrosis Registry.

23. **Mitsuaki Kawashima.** Association between Cytomegalovirus (CMV) and Chronic Lung Allograft Dysfunction (CLAD) in Lung Transplant Recipients.

25. **Mohammad Hashim.** Disposal Recommendations for Inhaler Products in Canada.


28. **Raina Ladha.** Pre-Motor Cholinergic Circuitry Controlling the Upper Airway Musculature In-Vivo.

29. **Jeffrey Lam Shin.** Barriers and Enablers to Objective Testing for Asthma and COPD in Primary Care: A Systematic Review Using the Theoretical Domains Framework.

30. **Jeffrey Lam Shin.** Developing a Decision Aid for a New Asthma Treatment Paradigm: Results from a Rapid-Cycle Design Study.

31. **Daniel Lee.** The Impact of Chronic Rhinosinusitis on the Health-Related Quality of Life among Adult Patients with Cystic Fibrosis.

33. **Jesse Lu.** An automated machine learning classifier to predict prognosis in acute exacerbations of chronic obstructive pulmonary disease.

34. **Jason McConnery.** Pediatric acute asthma burden was reduced during the COVID-10 pandemic lockdown: a single site experience.

35. **Sajad Moshkelgosha.** Pulmonary macrophage subsets associated with lung allograft dysfunction revealed by single-cell RNA sequencing.

36. **Sajad Moshkelgosha.** Validation of CD4+ CD57+ PD1+ T Cells in Bronchoalveolar Lavage as a Biomarker of Lung Allograft Dysfunction.

37. **Sepehr Niakani.** Characterization and Relative Efficacy of Muscarinic Receptor Antagonism at the Hypoglossal Motor Nucleus to Block Inhibition of Tongue Motor Activity.

38. **Michael Nicholson.** Pulmonary Rehabilitation in Cystic Fibrosis Lung Transplant Candidates.


40. **Shaun Ong.** Fibrotic interstitial lung disease survival in a national Canadian registry.

41. **Natalka Parzei.** Glutamatergic pre-Bötzing complex neurons as potential targets to alleviate opioid-induced respiratory depression.
42. **Rayoun Ramendra.** Donor Airway Bile Acid as a Biomarker of Aspiration and Predictor of Post-transplant Outcomes.

45. **Sana Swaleh.** Contemporary Birth Rates of Cystic Fibrosis in Canada.

46. **Ambily Ulahannan.** Non-HLA Antibodies In Serum Prior To The Onset Of Chronic Lung Allograft Dysfunction.

47. **Anastasiia Vasileva.** Oscillometry Tracks Graft Injury Following Lung Transplant: Association With Acute Cellular Rejection And Chronic Lung Allograft Dysfunction (CLAD).

48. **Wallace Wee.** Investigating for laterality defects in primary ciliary dyskinesia.


51. **Lena Xiao.** Positional Therapy for the Treatment of Positional Obstructive Sleep Apnea in Children: A Pilot Study.

52. **Shenhab Zaig.** Mechanisms underlying opioid-induced respiratory depression and analgesia in larval zebrafish.

53. **Gabriella Scott.** Assessing Equity, Diversity, and Inclusion in HHT Research.

54. **Kristen Thompson.** Doxycycline Randomized Controlled Trial for Hereditary Hemorrhagic Telangiectasia - Study Design and Preliminary Results.

55. **Jenny Shi.** Autotitrating Continuous Positive Airway Pressure Titration Compared to Laboratory-based Polysomnography Titration for the Treatment of Obstructive Sleep Apnea in Children with Complex Chronic Conditions.

56. **Ambily Ulahannan.** Non-HLA Antibodies In Serum Prior To The Onset Of Chronic Lung Allograft Dysfunction.
Abstract #1

**The impact of lumacaftor-ivacaftor on health outcomes in Canadians with cystic fibrosis**

**Ghadah Alrehaili (1,2), Mathieu Gravel (3), Xiayi Ma (1), Jenna Sykes (1), Adele Coriati (1), Sanja Stanojevic (4), Lara Bilodeau (3) and Anne L. Stephenson (1,5,6)**

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5. Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street.
6. Keenan Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Canada.

**Introduction**: Cystic fibrosis (CF) results from a defect in the cystic fibrosis transmembrane modulator protein (CFTR). New therapies, called CFTR modulators, target the defective protein to improve its function. There is limited data on the effectiveness of these drugs on Canadian patients with CF in a real-world. The objectives of the study were to quantify the rate of change in lung function and nutritional status and rate of pulmonary exacerbation in those prescribed lumacaftor-ivacaftor (LUM-IVA).

**Methods**: This is a cohort study using Canadian CF Registry (CCFR) data from 2008 to 2019. Patients who were continuously prescribed LUM-IVA without switching to another CFTR modulator were included. Rate of annual change in FEV1 percent predicted (ppFEV1) and body mass index (BMI) percentile as well as the rate of pulmonary exacerbations were compared before and after initiation of the drug. A linear mixed-effects model with both random intercept and slope terms was used. Sub-group analysis consisted of subjects with severe lung disease defined as having at least two ppFEV1 measurements ≤ 40% within a two-year period prior to starting LUM-IVA.

**Results**: After starting LUM-IVA, there was an initial increase in ppFEV1 of 2.32 %pred (95% CI 1.57-3.08, p <0.001). There was no difference in the rate of decline in FEV1 comparing the pre- and post-treatment period (p=0.51). The BMI percentile increased by 1.15 %ile (95% CI 0.18-2.13, p= 0.021) after initiating LUM-IVA. The annual rate of BMI %ile improvement was significantly different in the post-period compared to prior to initiation of the drug (difference in BMI %ile of 1.54%/year, 95% CI 0.53-2.55, p= 0.0028). The rate of pulmonary exacerbations was not statistically significantly different before and after therapy (risk ratio 0.95, 95% CI 0.82, 1.11, p= 0.53). For those with severe lung disease (N=61), there was a statistically significant increase in ppFEV1 after starting LUM-IVA of 3.23 %pred (95% CI 2.12-4.34, p<0.001). The rate of decline in ppFEV1 was significantly slower in the post-period compared to the pre-period (0.71 %pred/year and 2.69 %pred/year respectively, 95% CI 1.12-2.83, p<0.001). There was no difference in the rate of change in BMI percentile in the pre- and post-treatment period (p=0.28).

**Conclusion**: Canadians with CF realized a small increase in lung function and nutritional status with LUM-IVA however the magnitude is of little clinical significance. LUM-IVA may slow disease progression in people with severe lung disease but its effectiveness in the Canadian CF population is modest.

**Acknowledgements**: Thank you to Cystic Fibrosis Canada for providing CF Registry data, individuals living with CF and their families who have consented to having their data collected in CF patient registries and CF clinic staff who input data into the registry.
Abstract #2

Impact of Particulate Matter Exposure on microRNA Expression and the Development of Allergic Airways Inflammation

Gisele Beier (1), Rosalinda Chen (1), Sarina Zhang (2), Angela Hin (2), Xiaomin Wang (2), Chung-Wai Chow (1, 2, 3), Jeremy A. Scott (1)

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2. Division of Respirology, Department of Medicine, University of Toronto, Toronto ON.
3. University Health Network, Toronto ON.

Introduction: Exposure to particulate matter (PM) air pollution can impact the regulation of inflammatory pathways in the lung. One such mechanism is through the upregulation/downregulation of microRNA (miRNA) expression, which affects gene expression through mRNA inactivation. Understanding how PM exposure affects miRNA expression and inflammatory responses will help to develop approaches to mitigate the harmful effects of air pollution. The objective is to determine the impact of pre-exposure to PM on miRNA expression in a mouse model of House Dust Mite (HDM) induced allergic airways inflammation.

Methods: Mice were initially exposed to intranasal saline, diesel exhaust particulate (DEP), or standard reference material (SRM; collected from a diesel forklift) over 6 weeks. After the final saline/PM exposure, mice underwent a previously established model of HDM-induced allergic airways inflammation. Twenty-four hours after the final exposure, mice underwent pulmonary function testing with the flexiVent prior to bronchoalveolar lavage to assess inflammation and lung harvesting to isolate mRNA. MiRNA were identified using NanoString and quantified using nCounter. MiRNA expression was correlated with functional and inflammatory outcomes.

Results: HDM sensitization and challenge led to increased airways responsiveness to methacholine (as determined by total respiratory resistance, central airways resistance, and peripheral tissue damping), as well as increased inflammatory cell infiltration into the lung. Prior exposure to PM (DEP or SRM) did not augment the allergic airways inflammation or hypercontractility to methacholine. MiRNA let-7c and 30a were both downregulated in response to PM exposure compared with the saline controls and the HDM model. The downregulation of both let-7c and miR-30a correlated inversely with changes in lung function (i.e., total lung volume capacity, central airways resistance, tissue damping, and elastance) and inflammatory indices.

Conclusion: Exposure to PM downregulated let-7c and miR-30a in saline models and in HDM models of allergic airways inflammation. Identification of these miRNA species’ gene targets will facilitate further understanding of the mechanism(s) underlying the adverse health impact of PM air pollution.

Acknowledgements: Funding: Ontario Thoracic Society – Lung Health Foundation.
Abstract #3

Phenotyping CLAD after single lung transplant: limits and prognostic assessment of the 2019 international classification system

Gregory Berra (1,2), Ella Huszti (3), Liran Levy (1,2), Mitsuaki Kawashima (1), Eyal Fuchs (2), Benjamin Renaud-Picard (1), Peter Riddell (2), Olivia Dias (2), Sri Rajagopala (2), Ambily Ulahannan (2), Rasheed Ghany (1), Lianne Singer (2), Jussi Tikkanen (1,2), Tereza Martinu (1,2)

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3. Biostatistics Research Unit, University Health Network, University of Toronto, Toronto, ON.

Introduction: Phenotyping chronic lung allograft dysfunction (CLAD) in single lung transplant (SLTX) recipients is challenging due to the native lung contribution to pulmonary function tests (PFT). We aimed to assess the prognostic performance in SLTX of the 2019 CLAD guideline classification, put forth by the International Society for Heart and Lung Transplantation.

Methods: In this retrospective cohort of adult, first, SLTX from 2009 to 2017, patients with persistent drop in FEV1>20% were assessed by 2 independent reviewers to determine CLAD status and phenotype (bronchiolitis obliterans syndrome [BOS], restrictive allograft syndrome [RAS], mixed, undefined, or unclassified phenotype). We specifically noted presence or absence of RAS-like opacities on imaging, consistent with persistent fibrosis, as described by the 2019 CLAD guidelines. Disagreements were resolved by a 3rd reviewer. Interobserver agreement (IOA) was calculated by Cohen’s Kappa. Association of CLAD phenotypes with time to death/retransplant, adjusted for age, sex, CMV mismatch and native lung condition, were assessed with Cox proportional hazards models.

Results: Out of 172 SLTX patients, 92 had a persistent drop in FEV1>20%, of whom 67 got a diagnosis of CLAD. We noted a moderate inter-observer agreement (IOA) for CLAD status (Kappa 0.69) and poor IOA for phenotype (Kappa 0.5). When applying the 2019 CLAD guidelines strictly (based on exact cut-offs for PFT, along with imaging), 34 patients had BOS (50.7%), 9 RAS/mixed (13.4%), 7 undefined (10.4%), and 17 unclassified (25.5%). We found no association of these strict phenotypes with time to death/retransplant (Fig A). When using adjudicated CLAD phenotypes, 31 patients had BOS (46.3%), 15 RAS/mixed (22.4%), 2 Undefined (3%), and 19 Unclassified (28.3%). Using these adjudicated phenotypes, RAS/mixed was significantly associated with higher risk of death/retransplant (HR 2.98, 95%CI [1.39-6.4]) (Fig B). Finally, the specific adjudication of RAS-like opacities had the best IOA (Kappa 0.73). Presence of RAS-like opacities was a strong predictor of death/retransplant (HR 2.3, 95%CI [1.2-4.5]) (Fig C).

Conclusion: PFT interpretation is challenging in SLTX. Using a classification relying more on imaging analysis that harboured good IOA, we obtained better prognostic performance than with using a strict application of published physiologic cut-offs. We recommend that future guideline iterations have specific criteria for SLTX patients, with a greater focus on imaging rather than physiological cutoffs.
Abstract #4

Excess healthcare utilization and mortality in younger adults with COPD

Alina J. Blazer (1), Rachel McGihon (2), Andrea S. Gershon (1,3,4)

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4. ICES, Toronto, ON.

Introduction: Chronic obstructive pulmonary disease (COPD) is a common chronic condition that places a large burden on healthcare systems. Generally considered a disease of older adults, COPD can also affect younger patients, but less attention has been paid to the clinical features of COPD in younger individuals. A common assumption is that COPD diagnosed earlier in life can be equated with a milder severity of disease. However, this has not been fully examined in a real-world population study. The objective of this study was to examine health services utilization and mortality in younger adults with and without COPD. Older adults were also examined as a comparison group.

Methods: A longitudinal, population cohort study was conducted using health administrative data from the 14 million diverse residents of Ontario, Canada. All younger adults (35 to 55 years) and older adults (>65 years) with COPD were identified using a validated case definition. Annual mortality and health services use (HSU) rates were calculated between 2006 and 2016 and compared between sexes, across age groups and to corresponding rates from the non-COPD 2016 Ontario population.

Results: Younger adults with COPD had significantly increased rates of HSU and mortality compared to the non-COPD population. All-cause emergency department (ED) visits, hospitalizations and all-cause outpatient visits were significantly higher in younger adults with COPD compared to their non-COPD counterparts. Rates of all-cause ED visits and all-cause outpatient visits among younger adults with COPD exceeded rates seen in older adults without COPD. Younger adults with COPD, however, had elevated mortality rate compared to those without COPD (5.6-fold greater rate for females, 4.5-fold greater rate for males), an elevation much more pronounced than in older people.

Conclusion: Our data demonstrates that younger adults with COPD experience significant morbidity and excessive mortality from their disease. This study provides further evidence that “early” COPD is not a benign entity. Clinical efforts should focus on targeting younger adults with COPD with earlier interventions that can improve their state of health and prevent further progression of their disease.

Acknowledgements: Supported by: Division of Respirology, Department of Medicine, University of Toronto.
Abstract #5

“Patients are the people who teach me the most” – Exploring resident perspectives on the development of physician-patient communication skills

Gabriel Burke (1), Lindsay Melvin (1,2), Shiphra Ginsburg (1,3)

1. Department of Medicine, University of Toronto.
2. Division of General Internal Medicine, University Health Network.
3. Department of Medicine, Sinai Health System.

Introduction: Physician-patient communication training is a vital component of medical education and an active area of research. Despite extensive literature on the potential efficacy of various communication training interventions, little is known about which training modalities residents find effective or how residents believe they learn to communicate with patients. We sought to understand resident perspectives on existing communication training and on their personal communication skills development.

Methods: We conducted one-on-one interviews with 15 Internal Medicine residents from all 3 years of the University of Toronto’s Internal Medicine program. Residents were asked to reflect on their communication skills development and to discuss their experiences with different methods of communication training. Interviews were conducted, transcribed, and analyzed iteratively using constructivist grounded theory.

Results: Residents credited the majority of their skills development to self-reflection on unsupervised interactions with patients, without guidance from an attending. Attendings’ contributions were still perceived as significant but primarily through role modelling, with little perceived learning coming from direct feedback on observed interactions. This was partly explained by residents’ proclivity to alter their communication styles when observed, rendering any feedback less relevant to their authentic practice, and by residents generally receiving positive feedback lacking in constructive features. Time constraints on inpatient services led many residents to develop communication styles that prioritized efficiency at the cost of patient-centeredness, which residents recognized as discordant with the tenets of planf medicine and sometimes caused feelings of guilt.

Conclusion: These findings suggest current models of resident communication training and assessment may lack validity due to an overreliance on observation by attendings and examiners, which fail to unearth the authentic and largely self-taught communication habits of residents. Further research is required to ascertain the feasibility and potential value of other forms of communication skills training and assessment, such as through patient feedback.

Acknowledgements: Funding for this project was received from the Mount Sinai Hospital Department of Medicine Research Fund.
Abstract #6

Previously diagnosed and undiagnosed COPD among lung cancer patients in Ontario

Stacey J Butler (1, 2, 3), Dr. Alexander Louie (3), Dr. Rinku Sutradhar (2, 4), Dr. Lawrence Paszat (2, 3, 4), Dr. Dina Brooks (5, 6), Dr. Andrea S Gershon (1, 2, 3, 7)

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Introduction: Lung cancer is the leading cause of cancer-related deaths in Canada, with the majority of people being diagnosed with stage IV disease. People with chronic obstructive pulmonary disease (COPD) have a higher risk of developing lung cancer and have worse outcomes when compared to people without COPD. Previous studies focus only on COPD that was diagnosed prior to lung cancer and screening programs rely solely on self-reported COPD to identify eligible high-risk individuals. This is problematic as COPD is often underdiagnosed in the community. We sought to characterize previously diagnosed and undiagnosed COPD in patients with lung cancer in Ontario.

Methods: We conducted a population-based study using health administrative data, which included all individuals diagnosed with lung cancer in Ontario between 2009 – 2018, who had information on stage in the Ontario Cancer Registry. We explored the timing of COPD diagnosis in relation to lung cancer to identify three cohorts; no COPD, previously diagnosed COPD (> 90 days prior to lung cancer) and undiagnosed COPD (within 90 days of lung cancer). We assessed the trends in COPD and stage of diagnosis over time using a Cochrane-Armitage test and compared sociodemographic and lung cancer characteristics among disease cohorts using standardized mean differences.

Results: There were 74,172 individuals with lung cancer included in the study. Overall, 55% of patients with lung cancer had coexisting COPD. The majority of COPD patients (81%) were diagnosed prior to developing lung cancer, with a median time between diagnoses of 11 years (IQR: 5 to 16 years). Undiagnosed COPD was common, affecting 1 in 10 lung cancer patients. There was no overall change in the proportion of people with COPD or diagnosed with stage IV disease during the study period. Many sociodemographic and cancer characteristics differed among the disease cohorts. Most notably, people with previously diagnosed COPD were older, had more comorbidities and were from lower income quintiles compared to people without COPD. There were fewer patients with previously diagnosed (47%), or undiagnosed COPD (49%) with stage IV disease, compared to people without COPD (58%).

Conclusions: COPD impacts the majority of lung cancer patients and a significant number of people have undiagnosed disease. Further research is needed to explore the association between COPD and stage of lung cancer at diagnosis and also to determine the impact of COPD on the quality of patient care and health outcomes.

Acknowledgements: Supported By: Division of Respirology, Department of Medicine, University of Toronto.
Abstract #7

Association of obstructive sleep apnea with thoracic fluid volume and small airways narrowing in asthma during sleep

Xiaoshu Cao (1,2), Cristina O. Francisco (2), Nasim Montazeri G. (1,2), Susan M. Tarlo (3,4), Matthew B. Stanbrook (3,4), T. Douglas Bradley (2,4), Azadeh Yadollahi (1, 2)

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4. Division of Respirology, Department of Medicine, University of Toronto.

Introduction: Obstructive sleep apnea (OSA) is prevalent in asthma patients and is related to asthma severity. This suggests a pathophysiological link between the two. Since exaggerated negative pleural is generated during obstructive apneas, it could draw more fluid into thorax that could cause small airway narrowing. Previously, we showed that generation of negative pleural pressure during Mueller maneuvers to simulate obstructive apneas, drew fluid into the thorax, and narrowed small airways. We therefore hypothesized that patients with asthma and co-existing OSA (apnea-hypopnea index≥10) will have a larger overnight increase in thoracic fluid volume (TFV) and a greater degree of small airway narrowing, than those without OSA.

Methods: Participants underwent overnight polysomnography. Before and after sleep, we measured TFV and respiratory system reactance at 5Hz (X5), as an index of small airway narrowing, using oscillometry. Changes in all variables between the two groups were compared using analysis of covariance (ANCOVA).

Results: Compared to the non-OSA group, participants with coexisting OSA had significantly greater overnight increases in TFV (162.6±46.7 vs 47.8±48.3, P = 0.009) and greater narrowing of small airways (-1.2±0.7 vs 0.2±0.3, P = 0.013).

Conclusion: These results suggest that increases in TFV resulting from exaggerated negative pleural pressure swings during obstructive apneas are one mechanism by which OSA could worsen asthma at night.

Acknowledgements: Ontario Graduate Scholarship, Ontario Thoracic Society, Canadian Respiratory Research Network.
Abstract #8

Mortality and Cardiovascular Hospitalizations in Hemodialysis Patients with Sleep Apnea

Eric Carelli (1), Christopher T. Chan (2), Clodagh M. Ryan (2,3), Douglas T. Bradley (2,3), Owen D. Lyons (2,3,4)

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2. Department of Medicine, University Health Network.
3. Sleep Research Laboratory, University Health Network Toronto Rehabilitation Institute.
4. Department of Medicine, Women's College Hospital.

Introduction: Untreated sleep apnea (SA) is a risk factor for long-term cardiovascular (CV) disease and mortality. Patients with end-stage renal disease (ESRD) are at increased risk of SA, with rates of sleep-related breathing disorders as high as 50-60%. Despite the high prevalence of SA in the ESRD population, and the known CV risks of both CKD and untreated SA, there is a paucity of research evaluating the health outcomes of hemodialysis patients with SA. The primary objective of this study was to determine the association between the presence of moderate to severe SA and the risk of death and CV hospitalization in ESRD patients on hemodialysis. The secondary objective was to determine the polysomnographic predictors of mortality and CV hospitalization.

Methods: This was a retrospective cohort study of adult ESRD patients on hemodialysis who underwent a polysomnogram (PSG) between August 2008 and December 2015. Eligible patients were divided into two groups based on the presence of moderate to severe SA (apnea hypopnea index ≥15). Medical charts were reviewed for the occurrence of death or CV hospitalization within five years of the initial PSG. The Kaplan-Meier method was used to generate survival estimates and Cox proportional hazards regression analysis was performed to determine hazard ratios (HR) for the composite outcome of death or CV hospitalization.

Results: 65 patients were recruited, of which 45 (69.2%) had moderate to severe SA. A total of 18 composite events occurred: 17 in the moderate to severe SA group and 1 in the control group (p=0.007). The unadjusted HR for death or CV hospitalization was 9.10 (95% CI 1.21-68.46, p=0.03). Multivariate analysis identified age and gender as the only parameters with a statistically significant association with death or CV hospitalization. Moderate to severe SA was associated with an adjusted HR of 0.86 (95% CI 0.08-9.65, p=0.90). The presence of significant nocturnal hypoxemia (≥10% of total sleep time with oxyhemoglobin saturation <90%) was associated with an increased risk of death or CV hospitalization in multivariate analysis, with an adjusted HR of 4.55 (95% CI 1.18-17.58, p=0.03).

Conclusion: This retrospective cohort study demonstrated that the presence of significant nocturnal hypoxemia surpasses AHI as a predictor of the 5-year risk of mortality or CV hospitalization in ESRD patients with SA. Oxygenation parameters should be more strongly considered in the evaluation, treatment and prognostication of ESRD patients with SA. Further prospective research is required to investigate these associations.

Acknowledgements: Thank you Dr. Owen Lyons for your excellent mentorship, dedication and support.
Abstract #9

Assessment of Cardiac Autonomic Dysfunction in Chronic Thromboembolic Pulmonary Hypertension

Karan Chohan (1), Indranil Balki (1), Fatemeh Bavghar-Zaeimi (2), Sahar Nourouzpour (3), John T Granton MD (3,4), John Thenganatt (1,4), Micheal McInnis (5), Karen McRae (1,6), Laura Donahoe (1,2), Marc de Perrot (1,2), Dmitry Rozenberg (1,3)

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Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by symptomatic pulmonary vascular thrombi and is associated with significant morbidity. Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH and identifying novel prognostic markers may help inform post-PEA outcomes. One potential marker is cardiac autonomic dysfunction (AD), which represents a state of sympathetic hyperactivity, associated with adverse outcomes in cardiopulmonary populations, but not evaluated in CTEPH. We aimed to evaluate the association between cardiac AD and pre-PEA symptoms, exercise capacity, pulmonary vascular hemodynamics, and post-operative hospital outcomes.

Methods: Retrospective single-center cohort study of 110 CTEPH patients who underwent PEA (1/2014-12/2017) and had a complete set of heart rate parameters from their six-minute walk test (6MWT). Cardiac AD was characterized as a heart rate recovery (HRR)≤12 beats after one-minute of recovery after the 6MWT, an accepted method in the cardiopulmonary literature. Pre-operative clinical characteristics, Charlson Comorbidity index (CCI), NYHA class, six-minute walk distance (6MWD), pulmonary vascular resistance (PVR), post-operative intensive care unit (ICU) and hospital length of stay (LOS) and discharge disposition were abstracted from charts. Differences and associations between abnormal and normal HRR were compared using t-tests, chi-squared, and multivariable regression.

Results: Amongst 110 CTEPH patients [age: 57±5, 51% female, BMI: 30.5±6.6 kg/m2] prior to PEA, 64 (57%) patients were observed to have abnormal HRR. Patients with abnormal HRR were older (63±13 vs 53±15 years, p=0.0003), more likely to be female (64% vs 41%), p=0.02) and have a higher CCI (2 IQR [1-3] vs 1 IQR [0-2], p=0.0004). Those with abnormal HRR had a lower pre-operative 6MWD (289±125 vs 449±135 meters, p<0.0001), higher proportion of NYHA Class 3-4 symptoms (91% vs. 57%, p<0.0001), and higher PVR (1155 IQR [809-1529] vs 702 IQR [505-979] Dynes.sec.cm-5, <0.0001). Abnormal HRR was associated with a longer median post-operative ICU stay (3 days, p=0.0002) and hospital LOS (6 days, p=0.003), but not independent of age, sex, and 6MWD. Pre-operative 6MWD (per 100 meters) was a better independent predictor of median ICU (-0.6 days, p=0.01) and hospital LOS (-1 day, p=0.046) than HRR. No association between abnormal HRR and post-PEA arrhythmias, pneumonia or discharge disposition was observed.
Conclusion: Cardiac AD is associated with pre-operative symptoms, disease severity, and decreased exercise capacity. However, pre-operative 6MWD was a better predictor of post-operative hospital LOS. Future investigation is needed to evaluate whether HRR can be utilized in the post-operative period as a marker of cardiac function and functional recovery.

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Abstract #10

International comparison of survival in Cystic Fibrosis between Canada, France and Australia.

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Introduction: The median age of survival estimated for people living with CF varies between countries. Canadians living with CF have a 10-year survival advantage compared to people living in the US even after accounting for multiple health-related factors (Stephenson et al, Annals Int Med, 2017). These data suggested that the healthcare system (multi-payer vs. single payer system) may contribute to the survival gap. In this study, we aim to compare outcomes between Canadians with CF and people living in countries that have comparable healthcare systems (universal and government-funded), such as France and Australia.

Methods: This population-based study utilized data from established national CF registries, in Canada, France and Australia between 2012 and 2016. Each variable in the respective registries was evaluated to create harmonized definitions. Period survival analysis was used to estimate median age of survival. The risk of death was compared between countries, after adjusting for patient and clinical characteristics, using a multivariable Cox proportional hazards model.

Results: Between 2012 and 2016, data on 4881 Canadian, 7329 French and 3896 Australian individuals with CF were available. Our preliminary results suggest that the overall median age of survival was 52.6 years (95% CI: 50.4-56.8) for Canada, 60.5 years (95% CI: 54.4-71.2) for France and 53.3 (95% CI: 47.5-60.3) for Australia. When adjusting for known prognostic variables (sex, PI, CF related diabetes, age at diagnosis/newborn screening and lung status), we observed that people in Canada (HR 1.47, 95% CI: 1.22-1.78, p <0.001) and Australia (HR 1.37, 95% CI: 1.1-1.69, p =0.004) are at higher risk of death than people in France. There was no evidence of a difference in the risk of death between Canada and Australia (HR 1.08, 95% CI: 0.86-1.35, p=0.51). Analyses are being updated using data up to 2019.

Conclusion: We observed differences in the median age of survival and risk of death between countries with comparable healthcare systems, suggesting that there may be modifiable factors that could explain the observed differences. Further analysis will be important to understand the factors that explain the disparities in outcomes between countries.

Acknowledgements: We thank CF patients and their families. Supported by Breathe Post-Doctoral Fellowship from The Canadian Lung Association, a Cystic Fibrosis Canada research grant and the Vaincre la Mucoviscidose research grant.
Abstract #11

The Impact of the High Emergency Lung Transplantation program in Cystic Fibrosis in France: insight from a comparison with Canada

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Introduction: France implemented a high emergency lung transplantation (HELT) program nationally in 2007. A similar program does not exist in Canada. The objectives of our study were to compare health outcomes within France as well as between Canada and France before and after the HELT program in a population with Cystic Fibrosis (CF).

Methods: This population-based cohort study utilized data from the French and Canadian CF registries. A cumulative incidence curve assessed time to transplant with death without transplant as competing risks. The Kaplan-Meier method was used to estimate post-transplant survival.

Results: Between 2002 and 2016, there were 1075 (13.0%) people with CF in France and 555 (10.2%) people with CF in Canada who underwent lung transplantation. The proportion of lung transplant increased in France after the HELT program was initiated (4.5% vs. 10.1%) whereas deaths pre-transplant decreased from 85.3% in the pre-HELT to 57.1% in the post-HELT period. Between 2008-2016, people in France were significantly more likely to receive a transplant (Hazard Ratio (HR) 1.56, 95% CI 1.37-1.77, p<0.001) than die (HR 0.55, 95% CI 0.46-0.66, p<0.001) compared to Canada. Post-transplant survival was similar between the countries and there was no difference in survival when comparing pre- and post-HELT period in France.

Conclusion: Following the implementation of the HELT program, people living with CF in France were more likely to receive a transplant than die. Post-transplant survival in the post-HELT period in France did not change compared to the pre-HELT period, despite potentially sicker patients being transplanted, and is comparable to Canada. Further studies are needed to better understand the differences between the countries and whether or not a similar prioritization strategy such as the HELT program would be advantageous in countries that have different geographical distribution and healthcare systems.

Acknowledgements: We thank CF patients and their families. Supported by Breathe Post-Doctoral Fellowship from The Canadian Lung Association, a Cystic Fibrosis Canada research grant and the Vaincre la Mucoviscidose research grant.
Abstract #12

Long-term impact of COPD on postoperative cardiorespiratory morbidity and mortality: a population cohort study

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Introduction: COPD is a common respiratory comorbidity encountered among surgical patients. While previous studies have examined the association between COPD and short-term post-operative morbidity and mortality outcomes, mainly in small cohorts, there remains a paucity of data with regards to the long term post-operative outcomes in patients with COPD at a population level. Objective: To describe risk of mortality and cardiopulmonary complications in the year following major elective non-cardiac surgery (index surgery) in patients with compared to those without COPD in Ontario, Canada.

Methods: This is a retrospective, real-world cohort study of people undergoing major non-cardiac elective surgery in Ontario between April 2005 and March 2015. All people equal to or greater than 35 years were followed for one year following their index surgery for death and cardiopulmonary complications. People with physician diagnosed COPD were identified using a previously validated case definition. Logistic regression was performed to compare the odds of outcomes in people with COPD and those without adjusted for demographics, comorbidity, and surgery subtype.

Results: A total of 630,057 patients were included of whom 7.3% had COPD. Of those, 76% were equal to or greater than 65 years and 49% were men. Odds ratios of death and cardiopulmonary complications in patients with compared to those without COPD are shown in Table 1.

Conclusion: Patients with COPD have increased odds of death and all cardiopulmonary complications in the year following surgery.
Table 1: Adjusted odds of various outcomes within one year after major non-cardiac elective surgery in people with compared to people without COPD in Ontario, Canada.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted* Odds Ratio</th>
<th>Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.69</td>
<td>(1.59 – 1.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Respiratory and Cardiovascular Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Complications</strong></td>
<td>2.83</td>
<td>(2.76 – 2.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pneumonia Hospitalization</td>
<td>2.87</td>
<td>(2.72 – 3.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Re-intubation Hospitalization</td>
<td>1.55</td>
<td>(1.43 – 1.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiratory Failure Hospitalization</td>
<td>3.05</td>
<td>(2.65 – 3.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Cardiovascular Complications</strong></td>
<td>1.06</td>
<td>(1.03 – 1.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac Arrhythmia Hospitalization</td>
<td>1.29</td>
<td>(1.23 – 1.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary Artery Disease Hospitalization</td>
<td>1.33</td>
<td>(1.23 – 1.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart Failure Hospitalization</td>
<td>1.65</td>
<td>(1.56 – 1.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic Stroke Hospitalization</td>
<td>1.21</td>
<td>(1.09 – 1.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>1.61</td>
<td>(1.31 – 1.97)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abstract #13

Donor neutrophils and B cells in EVLP perfusate are associated with severe primary graft dysfunction

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Introduction: Primary graft dysfunction (PGD) remains a major obstacle to lung transplantation (LT) success and is classified as severe (PGD3) in 10-15% of all LT recipients. Ex vivo lung perfusion (EVLP) allows for evaluation of donor lungs prior to LT and measurement of circulating cells and soluble factors in the perfusate. The contributions of donor cells to PGD are unknown, and whether specific cells might confer a risk of PGD is unclear. We hypothesized that larger quantities of donor myeloid cells in EVLP perfusate might predict PGD3.

Methods: In this retrospective study, we selected consecutive clinical EVLP cases and grouped them based on PaO2/FIO2 (P/F) ratio at 72h post-LT, resulting in two groups: PGD3 (n = 33, P/F = 183 ± 48mmHg) and PGD0/1 (n = 25, P/F = 395 ± 71mmHg). Cryopreserved perfusate cells from the first and last hour of EVLP were subjected to multiparameter flow cytometry to identify major leukocyte populations. Time and PGD-dependent differences were assessed by two-way ANOVA with post-hoc testing adjusted for multiple comparisons.

Results: In the first hour of EVLP, the total cells/ml was higher in the PGD3 group compared to PGD0/1 (12.1 x 10^5 versus 8.4 x 10^5 cells/ml, p = 0.0573) - the cell/ml decreased in both groups to similar densities by the end of EVLP. In the PGD3 group, several leukocytes were significantly higher than in the PGD0/1 group in the first hour, notably neutrophils (p = 0.0008) and B cells (p = 0.0103). In both cell types, the absolute number of cells decreased significantly over time (p < 0.0001) to match cell numbers similar to the PGD0/1 group. Macrophages and classical monocytes were also elevated in PGD3 group in the first hour, although this observation did not reach statistical significance.

Conclusion: Neutrophils and B cells in the 1-hour perfusate are associated with PGD3 development at 72h post-LT. While these findings suggest that higher numbers of these donor cells may play a role in PGD pathogenesis, PGD3 developed even though these populations were reduced by the end of EVLP. Studies of cellular activation states will be conducted to validate these findings and explore donor cellular contributions to PGD.
Abstract #14

**Time to positive culture detection as a predictor of Mycobacterium avium pulmonary disease severity**

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3. Department of Respiratory Medicine, West Park Healthcare Centre.

**Introduction:** The decision to initiate treatment for Mycobacterium avium pulmonary disease (MAC-PD) balances clinical, radiologic, microbiologic and personal factors, often seeking to predict which patients will experience progression. Additional evaluative tools are needed. Time to positive sputum culture detection in broth media (TTP) is used in tuberculosis management, correlating inversely with baseline bacterial inoculum and directly with early treatment response, culture conversion, and reduced risk of relapse. TTP has not been investigated in MAC-PD, therefore we explored its association with infection severity and early treatment response.

**Methods:** We undertook a retrospective cohort study of patients with ≥2 sputum cultures positive for M. avium at Toronto Western Hospital NTM clinic from January 1, 2015 until December 31, 2019. Included patients had an ‘index’ sputum specimen during the study period, a CT scan within 6 months, and were untreated for ≥6 months prior to index sputum. TTP was estimated from the date of laboratory receipt of the specimen to the date of culture positivity confirmation, using the BACTEC MGIT 960. TTP was tested for association with markers of infection severity (MAC-PD, bronchiectasis, cavitary disease, treatment initiation by 3 and 6 months, AFB smear) and treatment response using Mann-Whitney U, Spearman’s Correlation Coefficient, and Wilcoxon signed-rank tests, as appropriate. We explored a threshold TTP that could identify significant NTM disease.

**Results:** We included 125 patients with mean (SD) age 68.5 (12.5) years, 69% female, 65% fulfilled disease criteria. Median TTP was 12 days (IQR 10-15; range 6-44). Treatment occurred in 53 patients. TTP and AFB smear grade were negatively correlated (r -0.58, p<0.001). TTP was significantly associated with presence of NTM disease (p=0.03), AFB smear positivity (p<0.001), and treatment initiation by 3 months (p=0.01) and 6 months (p=0.03). A threshold TTP of ≤10 days was associated with MAC-PD (p=0.02), AFB smear positivity (p<0.001), treatment by 3 months (p=0.003) and 6 months (p=0.003). After three and six months of treatment the median change in TTP was +8 days (IQR 1-undefined; p<0.001) and +7 days (IQR 0-undefined; p=0.001) respectively.

**Conclusion:** TTP is associated with bacterial burden at baseline and increases in response to treatment. Additionally, TTP correlates with infection severity and a threshold of ≤10 days may be useful in predicting presence of MAC-PD and the need for treatment. As a readily available evaluative tool without additional cost or labour, further exploration of TTP in larger patient cohorts is warranted.
Abstract #15

Association between Esophageal Dysmotility and Long-term Outcomes in Lung Transplant Recipients

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Introduction: Esophageal dysmotility is very common in patients with end-stage lung disease and post lung transplantation and is thought to predispose to allograft injury through higher risk of aspiration. At our center, we routinely test lung transplant recipients for esophageal dysmotility with High Resolution Manometry (HRM) at 3 months post-transplant. We hypothesize that lung transplant recipients (LTRs) with significant esophageal dysmotility are more likely to develop lung injury leading to CLAD and death.

Methods: Among 1753 LTRs transplanted at our center between July 2000 and June 2018, we retrospectively analyzed 426 patients who had HRM with a 24 hour-pH impedance study available post-transplantation. Esophageal hypomotility was defined as >= 30% of failed and/or simultaneous esophageal contractions, while esophageal hypermotility was defined as evidence of higher amplitude on HRM. Cox proportional hazards models adjusted for age, sex, native lung disease, CMV matching, and transplant type (single vs double) were used to determine the association between esophageal dysmotility and death/retransplant or CLAD.

Results: Esophageal hypomotility and hypermotility was found in 120 (28%) and 22 (5%) patients, respectively. Mild, moderate, and severe hypomotility was found in 58 (48%), 14 (12%), and 48 (40%) patients, respectively. In multivariate analyses, esophageal hypermotility or hypomotility was not associated with CLAD (HR 0.59 [95% CI 0.21-1.60]; HR 0.79 [95% CI 0.52-1.19]). or death (HR 0.53 [95% CI 0.16-1.68]; HR 0.62 [95% CI 0.37-1.03]). The risk of CLAD or death did not vary by severity of hypomotility.

Conclusion: In a large single-center lung transplant cohort study, we have determined that esophageal dysmotility is not associated with CLAD or death. Concurrent GI co-morbidities, such as reflux and gastroparesis, may play a role in modifying this risk. Additionally, center-specific approaches to patient selection and/or treatment may be related to outcomes and will be further assessed in future studies.
Figure 1. Survival curves showing time to CLAD development stratified by esophageal motility results.

Figure 2. Survival curves showing survival probability over time stratified by dysmotility results.
Abstract #16

How Ultrasound Can Predict Sarcopenia in Lung Transplant Candidates


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Introduction: Sarcopenia is an important predictor of clinical outcomes in lung transplant candidates. Dual-energy X-ray absorptiometry (DXA) is the gold standard to determine appendicular lean mass (ALM), a primary marker of sarcopenia, however it is not always feasible to conduct. Muscle ultrasound can be used to quantify muscle and may be a simpler, alternative tool for detecting sarcopenia. Objectives: To determine the most parsimonious model from ultrasound to predict ALM index (ALMI) from D-XA and to determine cut-points for low muscle size from ultrasound.

Methods: Cross-sectional study of adult lung transplant candidates from a single centre. Subjects underwent B-mode ultrasound of the dominant leg to assess muscle layer thickness of quadriceps (sum of rectus femoris (RF), vastus intermedius and lateralis), and gastrocnemius, RF cross-sectional area (CSA) and tibialis anterior (TA) CSA. Ultrasound measures of muscle size were normalized to limb length. ALMI (kg/m²) was assessed with DXA, and used to define sarcopenia using cut-points of ≤7.26 kg/m² for men and ≤5.45 kg/m² for women. Hierarchical, stepwise multilinear regression analysis was used to predict ALMI from ultrasound measures and demographic variables (age, sex, diagnosis). Three multilinear regression analysis were developed based on the feasibility of the ultrasound imaging protocol (number of muscles and subject position). A receiver operating characteristic (ROC) curve was used to determine the ultrasound cut-points for low muscle size.

Results: 61 lung transplant candidates were included (52% female, median (IQR) age= 63 [55–67] years, BMI= 25.4 [21.7 – 28.2] kg/m², diagnosis: 48% ILD, 34% COPD, 18% other diseases). 53% of females and 52% of males had low muscle quantity based on ALMI criteria. Age and diagnosis were not correlated with ALMI. All regression models were associated with ALMI: five-muscle model [quadriceps thickness (sum of RF, vastus intermedius and lateralis thickness) + gastrocnemius thickness + TA CSA + sex; R² = 0.799, p < 0.001]; four-muscle model (quadriceps thickness + TA CSA + sex; R² = 0.778, p < 0.001) and two-muscle model (RF CSA + TA CSA + sex; R² = 0.741, p = 0.001). The cut-point for low muscle size, based on the two-muscle regression model was ≤ 0.257 cm² for females and ≤ 0.294 cm² for males.

Conclusions: Lower limb muscle ultrasound can be used to predict muscle size in lung transplant candidates using as few as two muscles. This method may be applicable in clinical/research settings.

Acknowledgements: Canadian Institutes of Health Research – CIHR.
Abstract #17

Ophthalmologic assessments in patients with newly diagnosed sarcoidosis: an observational study from a universal healthcare system

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Introduction: Consensus guidelines for the management of sarcoidosis recommend screening eye examinations for all patients, even in those without ocular symptoms. We aimed to determine the proportion of sarcoidosis patients that complete ophthalmologic evaluations and factors associated with their performance.

Methods: We identified patients with sarcoidosis using population health services data from Ontario, Canada between 1991 and 2019. Sarcoidosis was defined by ≥ 2 physician visits for sarcoidosis within a two-year period. Ophthalmologic evaluations were based on an optometrist or ophthalmologist visit within the year prior or two years following the diagnosis. We estimated correlations between the number of eye care professionals and proportion of sarcoidosis patients completing ophthalmologic assessments within regional health units. We evaluated for associations between ophthalmologic screening and patient characteristics using multivariable logistic regression.

Results: We identified 21,679 patients with sarcoidosis in Ontario. An ophthalmologic evaluation was performed in 14,751 (68.0%), with a similar number of individuals seeing ophthalmologists and optometrists (43.7% vs. 42.2%). The percentage of sarcoidosis patients undergoing an ophthalmologic evaluation within corresponding regional health units was moderately correlated with the number of practicing ophthalmologists (r = 0.64, p=0.01), but not the number of optometrists (r = 0.08, p = 0.77). Patients who were older [OR per year 1.02 (95% CI 1.01-1.02), p<0.001] and female [OR 1.54 (95% CI 1.44-1.63), p<0.001] were more likely to complete ophthalmologic evaluations. Immigrants to Canada were less likely to undergo ophthalmologic assessments [OR 0.66 (95% CI 0.60-0.73), p<0.001].

Conclusions: Most patients with sarcoidosis complete ophthalmologic examinations, though a substantial proportion does not. Young adults, men and immigrants were less likely to complete ophthalmologic evaluations. Limited access to ophthalmologists may at least in part explain why some sarcoidosis patients fail to complete ophthalmologic screening.
Abstract #18

The Role of Somatostatin-Expressing Cells in Opioid-Induced Respiratory Depression

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3. Division of Respirology, Department of Medicine, University of Toronto.

Introduction: Opioids have the ability to cause respiratory depression, a severe decline in respiratory rate that can be lethal with overdose. While key brainstem respiratory regions have been shown to play a role in respiratory depression by opioids, the cells involved remain unknown. One region of interest is the preBötzinger Complex, a site that mediates respiratory depression and contains a subgroup of somatostatin (SST)-expressing cells that are required to maintain normal breathing. We aimed to determine the role of SST-expressing cells in respiratory depression by opioids. We hypothesized that deletion of mu-opioid receptors (MORs) in SST-expressing cells will prevent opioid-induced respiratory depression.

Methods: We developed transgenic knockout mice that lack MORs in SST-expressing cells (SST-MOR-/-) using Cre-lox recombination. SST-Cre/+ mice (Ssttm2.1(cre)Zjh/J) were bred with Oprm1fl/fl mice (Oprm1tm1.1Cgrf/KffJ) to produce SST-MOR-/- mice. We used in situ hybridization to determine whether MOR mRNAs are colocalized with SST mRNA in the brainstem of control (wild-type, SST-MOR+/+), MOR-/- and SST-MOR-/- mice. To determine the effect of removing MORs from SST-expressing cells, respiratory depression by intraperitoneal injection of fentanyl (0.3mg/kg) was quantified in control (wild-type, SST-MOR+/+), MOR-/- and SST-MOR-/- mice. Respiratory rate was recorded using whole-body plethysmography.

Results: MORs were expressed in several brainstem regions regulating breathing such as the preBötzinger Complex, the Bötzinger Complex, the nucleus ambiguus, the Kölliker-Fuse nucleus, the locus coeruleus and the nucleus tractus solitarius, while SST and MORs were colocalized primarily in the preBötzinger Complex. Knockout of MORs in SST-expressing cells was confirmed by microscopy. Intraperitoneal injection of fentanyl (0.3mg/kg) induced a significant respiratory rate depression in wild-type (p<0.001, n=9), MOR-/- (p<0.05, n=7) and SST-MOR-/- (p<0.001, n=8) mice.

Conclusion: SST and MORs are colocalized in the preBötzinger Complex while MORs are expressed in other key brainstem respiratory sites. Preliminary data suggests that MORs in SST-expressing cells are not required for fentanyl-induced respiratory depression. Our previous work showed that arousal state can affect the severity of respiratory depression by opioids. For this reason, we are currently investigating the impact of arousal state (active versus inactive) on opioid-induced respiratory depression in control, MOR-/- and SST-MOR-/- mice.

Acknowledgements: Research support was provided through the Canadian Institutes of Health Research and AF was supported by an Ontario Graduate Scholarship.
Abstract #19

Identification of Novel microRNAs Regulating Skeletal Muscle Regeneration in Sustained Intensive Care Unit Acquired Weakness

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Introduction: Intensive care unit acquired weakness (ICUAW) is a complication of critical illness characterized by skeletal muscle wasting and impaired contractile function that may persist for years after ICU discharge, resulting in physical disability. Satellite cell loss and dysregulation of gene co-expression networks that control muscle repair and regeneration are present in critical illness survivors with persistent muscle wasting and weakness. MicroRNA (miRs) regulate gene expression, at the post-transcriptional level by affecting the translation or degradation of messenger RNA (mRNA). We sought to identify miRs that regulate the failure of muscle regeneration in critical illness survivors with sustained ICUAW. Hypothesis: Alterations in miR expression mediate aberrant expression of muscle regenerative genes post-ICU discharge, inducing sustained muscle wasting and weakness vs recovery in critical illness.

Methods: From a cohort of critically ill patients (n=14), skeletal muscle strength, mass, and physical function were measured and whole-transcriptome miR and mRNA expression was determined in quadriceps muscle biopsies at Day 7 and Month 6 post-ICU discharge. We then conducted an integrated miR-mRNA analysis to identify dysregulated miR/gene pairs that were robustly correlated with sustained muscle wasting in ICUAW and evaluated their impact on myoblast proliferation and differentiation in vitro. The highest ranking, differentially expressed, miRs identified in our miRNA/mRNA analysis were selected for in vitro study. Candidate miRs were overexpressed and inhibited in AB1167 human myoblasts and their influence on myoblast proliferation and differentiation were subsequently determined by quantification of cell counts, Ki67 nuclear localization, and expression of proliferating cell nuclear antigen, and myosin heavy chain.

Results: At 6 months post-ICU discharge, a fourteen-miR expression signature distinguished patients with a significant increase in muscle mass from those with sustained atrophy. miRs-490-3p and 744-5p, both increased in patients whose quadriceps size normalized, were each found to regulate up to 4% of the muscle transcriptome. miR-490-3p overexpression significantly reduced AB1167 myoblast proliferation, and induced contact independent myoblast differentiation to mature myotubes. miR-744-5p overexpression attenuated myoblast differentiation.

Conclusion: MicroRNA profiling identified key miRs involved in the regulation of muscle weakness at Day 7 and in the recovery of muscle mass at 6M post-ICU discharge. We identified miR-490-3p and 744-5p as novel regulators of myoblast proliferation and differentiation, which may play a causative role in the pathogenesis of sustained ICUAW.
Abstract #20

Fatherhood in men with cystic fibrosis: a survey of the knowledge, opinions, and experiences regarding family planning

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Introduction: Approximately 98% of men with CF exhibit obstructive azoospermia due to congenital bilateral absence of the vas deferens resulting in infertility. While there are several methods through which men with CF can still become fathers, the awareness and use of these options are not well characterized. This study aims to understand the knowledge of available options, determine what reproductive methods are currently used and why, and describe what factors influence the choice of men with CF to become fathers.

Methods: This qualitative cross-sectional study utilized an anonymous online survey sent to 193 male patients followed at the Toronto Adult CF Centre (St. Michael’s Hospital) between October 2020 and January 2021. Data obtained from 106/193 (55%) respondents were analyzed.

Results: Respondents were highly aware of assisted reproductive techniques (ART) (87/98, 89%), artificial insemination using donor sperm (AID) (69/98, 70%), and adoption (77/98, 79%). Out of 93 respondents over the age of 25, 35 (38%) reported having at least one child. Of the collective 60 children, 70% were biological, with 38 (63%) conceived using ART. Respondents reported: “the desire to have a child that shares my DNA” (37/58, 64%), “cost associated with fertility treatment (i.e. IVF and AID)” (36/58, 62%), and “concern about passing on my CF mutation to any biological children” (30/58, 52%) as factors influencing the chosen method. Despite the high cost, 77% of respondents (27/35) had at least one child through IVF. Of the 58 men (62%) who were not fathers, the 33 men (58%) who did not plan on having any children identified lack of interest (23/33, 70%), and “concern about how living with CF will affect parenting ability” (17/33, 52%) as key factors.

Conclusion: Most men with CF are aware of the different methods of becoming fathers. One third of respondents had children, with the majority having at least one biological child conceived through IVF. Despite concerns of the high cost of fertility treatments and the perceived risk of passing on the CF gene, the desire to father biological children is a strong contributor in the decision process. For those who did not plan on having children, the impact of having CF on their ability to parent was a key concern. In the future, the use of highly effective modulators may significantly influence the decision to become a father.
Abstract #21

Lung Function in COVID-19 Intensive Care Unit (ICU) Survivors Assessed with Respiratory Oscillometry (Osc) and Conventional Pulmonary Function Tests (cPFT)

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Introduction: Early follow-up of COVID-19 patients demonstrate a primary restrictive defect with reduced diffusing capacity (DLCO) resembling defects observed in acute respiratory distress syndrome patients. The long-term pulmonary consequences of COVID-19 are unknown. Osc has been found to be more sensitive than cPFT for early diagnosis of chronic obstructive pulmonary disease, acute rejection after lung transplant and interstitial lung disease following environmental exposures. We hypothesize that Osc is more sensitive than cPFT in identifying pulmonary physiological abnormalities in those with sustained functional impairment post-COVID-19. The objectives of this study are to determine the prevalence of abnormal lung function up to 9 months post-COVID-19 and to compare cPFT with Osc in detecting respiratory dysfunction.

Methods: COVID-19 patients who survived ICU admission and were followed at the TGH post-recovery outpatient clinic are prospectively enrolled for quarterly Osc, cPFT, 6-Minute Walk Test and survey with the Borg CR10 Scale. Demographic and clinical data are extracted from electronic patient records.

Results: From August 20, 2020-April 18, 2021, we enrolled 31 patients. For the interim analysis, current smokers and those with pre-existing lung disease or missing data were excluded (n=13). For the 18 remaining patients (11 M/7 F; mean age 52±17), enrollment occurred 3 (n=10), 6 (n=6) and 9 months (n=2) post-infection. We had follow-up data 6 (n=1) and 9 months (n=5) post-infection. cPFT showed a primary restrictive defect with decreased DLCO at 3 months [%predicted total lung capacity=74±17, %predicted DLCO =82±26] which resolved by 9 months. The prevalence of cPFT abnormalities improved over time: at 3 months, 70% had restriction and 40% had reduced DLCO. By 6 and 9 months, 57% and 43% of patients had restriction and none had reduced DLCO. Osc was abnormal throughout: at 3 months, R5-19 (difference between respiratory resistance at 5 and 19 Hz) (median=1.07 [0.751-1.42] cmH2O∙s/L; normal < 0.80 cmH2O-s/L) and Ax (area of reactance) (median=12.7 [7.56-16.9] cmH2O/L; normal < 10 cmH2O/L) were high and remained so at 9 months (R5-19=1.09 [0.591-1.45]; Ax=14.8 [6.75-22.7]). The prevalence of abnormal Osc, pre-defined as abnormal R5-19 and/or Ax, was similar at 3 (80%), 6 (86%) and 9 months (71%). The Borg Scale indicated ongoing dyspnea (2.71±2.21) and fatigue (2.29±2.14) at 9 months.

Conclusion: Early findings in a small cohort of severe COVID-19 survivors revealed improvement in restrictive defects and DLCO by cPFT by 9 months. Osc remained abnormal, potentially explaining the persistent functional limitations identified by Borg dyspnea and fatigue measurements.

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Abstract #22

Real-world use of ivacaftor in Canada: A retrospective analysis using the Canadian Cystic Fibrosis Registry

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Introduction: Ivacaftor is a CFTR potentiator with demonstrated efficacy in clinical trials and has been rapidly adopted within the CF community. Given the uptake of ivacaftor in eligible people, identifying a comparator group not on modulators to measure effectiveness is difficult. We evaluated health outcomes in individuals with G551D and non-G551D genotypes on ivacaftor using real-world longitudinal data.

Methods: This population-based observational study compared clinical trajectories pre-post ivacaftor using the Canadian CF Registry from 2006-01-01 through 2018-12-31. Piece-wise linear mixed-effects models were used to compare lung function, nutritional status, pulmonary exacerbations, and Pseudomonas colonization pre- and post-ivacaftor. Multivariable models were used to adjust for confounding factors.

Results: Forced expiratory volume in 1 second (FEV1) increased significantly by 5.7 percent predicted (95% confidence interval (CI) 3.9, 7.5; p<0.001) after initiation of ivacaftor. FEV1 decline rate was attenuated to -0.30% (95% CI -0.9, 0.29; p=0.32) predicted/year post-ivacaftor, compared with -0.75% (95% CI -1.12, -0.37; p<0.001) predicted/year pre-ivacaftor, although this difference did not reach statistical significance. BMI percentiles also increased post-ivacaftor (6.57 percentiles, 95% CI 3.91, 9.24; p<0.001). Pulmonary exacerbations showed a nonsignificant reduction of 18% (RR 0.82, 95% CI 0.61, 1.11; p=0.19) and the odds of a positive sputum culture for Pseudomonas aeruginosa decreased in the post-ivacaftor period (odds ratio 0.44, 95% CI 0.30, 0.63; p<0.001).

Conclusion: This real-world, observational study demonstrated improvement in health outcomes in a broad population of people with CF. Additional studies are needed to evaluate the impact of ivacaftor on quality of life and survival.

Acknowledgements: We are grateful to Cystic Fibrosis Canada for providing registry data for this project. In addition, we would like to acknowledge and thank all of the CF patients and families in Canada who consent to be part of the Canadian CF Registry as well as the CF clinic staff who spend many hours inputting the data.
Abstract #23

Association between Cytomegalovirus (CMV) and Chronic Lung Allograft Dysfunction (CLAD) in Lung Transplant Recipients

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Introduction: Bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), and mixed are major phenotypes of CLAD. In previous, older studies, CMV viremia has been associated with reduced survival. We hypothesized that, in a more modern era of CMV prophylaxis, CMV viremia would remain associated with death, but also represent a risk factor for CLAD and specifically RAS/mixed phenotype.

Methods: This is a retrospective cohort study of all consecutive adult, first, bilateral-/single-lung transplants performed 2010-2016 who had ≥4 pulmonary function tests and ≥1 CMV-PCR measurement. CMV-PCR levels were divided into 3 categories: undetectable, <1000 IU/mL, and ≥1000 IU/mL. Risks for CLAD, RAS/mixed, or death/re-transplantation were assessed by Cox proportional hazards models using CMV-PCR as a time-dependent categorical variable, adjusting for variables listed in table.

Results: Of 645 patients, 257 developed CLAD (143 BOS, 44 RAS/mixed, 66 undefined/unclassified) and 388 were CLAD-free at last follow-up. In univariate analysis, CMV-PCR≥1000 IU/mL was a significant risk factor for CLAD (HR 1.33, p=0.05). In multivariate analysis, CMV-PCR was not a significant risk factor for CLAD, whereas CMV serostatus mismatch was (Table). CMV-PCR was not a significant risk factor for RAS/mixed (CMV-PCR<1000 IU/mL: HR 1.46, p=0.32. CMV-PCR≥1000 IU/mL: HR 1.43, p=0.33) in univariate analysis. Regarding time to death/re-transplantation, CMV-PCR was a significant risk factor in multivariate analysis, whereas CMV serostatus was not (Table).

Conclusion: CMV viremia was significantly associated with death/re-transplantation. Conversely, CMV viremia was not strongly associated with CLAD or RAS/mixed, while CMV serostatus mismatch was. CMV serostatus mismatch may have an impact on CLAD through mechanisms independent of viremia. In light of these paradoxical results, we are further assessing the relationship between immunosuppression, immune function, and CMV.
Abstract #24

A protective role of donor B cells against ischemia-reperfusion injury in a minor-mismatched mouse lung transplant model

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Introduction: We showed that recipient B cells are necessary for the development of chronic allograft fibrosis after ischemia-reperfusion injury (IRI) in a C57BL/10 (B10, H-2b)-to-C57BL/6 (B6, H-2b) minor alloantigen-mismatched mouse orthotopic lung transplant model. Whether donor-derived B cells play a specific role in this phenomenon is unknown. We hypothesized that donor B cells play a minimal role in the recipient.

Methods: We performed B10-to-B6 lung transplants with either prolonged (6h at 4°C followed by 45 min at 37°C and 15min anastomosis time) or minimal (1h at 4°C followed by 15min anastomosis time) antecedent storage using congenic donors and recipients. Donors were given anti-CD20 antibody or isotype control on day -2 (Fig 1A). Necropsies were performed at days +3 and +28. Allografts were histologically assessed in a blinded manner. Flow cytometry was used to evaluate immune cell populations at days 0 (pre-transplant donor samples), +3, and +28 (post-transplant samples).

Results: In the context of prolonged storage, anti-CD20 treatment was associated with early postoperative deaths not seen in the other groups (Fig 1B). At day 28, prolonged storage allografts exhibited fibrosis, with anti-CD20 treatment enhancing vascular fibrosis in surviving mice, but without impact on immune cell populations (Fig 1C). To better understand how anti-CD20 donor-treatment is impacting the allograft early post-transplant, we assessed the grafts at day 3: Both prolonged storage groups had severe IRI although, somewhat surprisingly, acute lung injury score was decreased by anti-CD20. Donor-derived B cells were reduced, and donor-derived neutrophils and monocytes were increased in the anti-CD20 group (Fig 1D).

Conclusion: Unexpectedly, our results suggest that donor-derived B cells have a protective role against IRI possibly via augmentation of neutrophils and monocytes in the donor graft. Further investigation is now underway.
Abstract #25

Disposal Recommendations for Inhaler Products in Canada

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Introduction: Three million Canadians have asthma and 800,000 have been diagnosed with COPD. Inhaler devices with bronchodilators, corticosteroids and combinations thereof, are the mainstay of therapy and are replaced frequently. They are typically packaged in cardboard boxes containing at least a plastic inhaler device and a Patient Medical Information (PMI) leaflet. We sought to describe the spectrum of manufacturer recommendations for the disposal of inhaler products in Canada.

Methods: The Health Canada Drug Product Database was used to obtain PMI leaflet and drug product monographs of inhaled products marketed or approved for use as of May 30, 2020. Nebulizer solutions, nasal sprays and products without monographs were excluded. Inspection of the documents for disposal recommendations was followed by an electronic search for relevant keywords. Disposal recommendations were qualitatively described and grouped by similarity. The frequencies of each recommendation were expressed as percentages.

Results: Documentation from 43 inhaler products from 11 different manufacturers were reviewed. Product monographs were most recently revised between 2013 and 2020. Disposal recommendations for inhaler devices in PMI leaflets were to: throw or discard (26, 60.5%), follow local disposal guidelines (2, 4.7%), not throw in household waste (1, 2.3%), discuss with pharmacist (7, 16.3%), return to pharmacy (2, 4.7%) or no recommendations made (8, 18.6%). Disposal recommendations for devices in product monographs excluding the PMI were to: throw or discard (25, 58.1%), follow local disposal guidelines (2, 4.7%), return to pharmacy (1, 2.3%) or no recommendation (15, 34.9%). Seven (16.3%) products had no disposal recommendations for the inhaler device on either the PMI leaflet or the product monograph. Information regarding the disposal of trays, pouches, wrapping, desiccants, capsules, blister packs, leaflets and boxes was missing or variable. No manufacturer recommended recycling inhaler devices or other package contents. Missing or inconsistent disposal information between PMI and drug monographs was noted for numerous products regardless of manufacturer, document publication year or number of pages.

Conclusion: Most inhaler products in Canada are either recommended to be thrown away or come with no guidance for disposal. Inhaler devices and their packaging contents likely end up in household waste. Given their periodic replacement, the environmental impact of plastic pollution attributable to inhaler devices is significant. Manufacturers should review the documentation of their inhaler products, consider the use of eco-friendly materials and update their PMI leaflets and monographs with consistent, safe and environmentally-friendly disposal recommendations.
Abstract #26

Development and Implementation of A National, Multimodal, Community-based, Culturally-sensitive Vaccine Confidence Knowledge Translation Strategy For a High Risk Community During the COVID-19 Pandemic: A Case Study of the Canadian Muslim COVID-19 Task Force

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Introduction: Among several public health measures used to combat the COVID-19 pandemic, newly developed vaccines were seen as foundational to mitigate the burden of illness and death worldwide. Racialized communities have been disproportionately impacted by the pandemic and these communities have traditionally demonstrated high rates of vaccine hesitancy. Canada’s 1 million Muslims are an ethno-racially and linguistically diverse community with disparate socioeconomic status and health literacy. Many are at-risk essential workers residing in multigenerational homes in hotspot regions and were unlikely to receive timely and reliable information in a culturally-sensitive manner amidst a rapidly evolving global health crisis, complicated by rampant misinformation.

Methods: Between December 2020 and May 2021, the Canadian Muslim COVID-19 Task Force (CMCTF) collaborated with Muslim health experts, faith leaders, grassroots community representatives and public health authorities to proactively develop and implement a vaccine confidence promotion strategy. A multimodal culturally-sensitive, intersectoral and iterative approach was employed, with interventions grounded in equity and accessibility for knowledge synthesis, dissemination and roll-out of COVID-19 vaccines.

Results: 4 position statements on different COVID-19 vaccines were developed to promote confidence with religious permissibility and provide guidance, as required. Faith leaders were highlighted as an influential priority vaccination group and were promoted alongside relatable health experts as champions as they received their vaccines. Community vaccine town halls in 6 languages and a train-the-trainer town hall for faith leaders were held. Health experts made appearances on ethnic media and a nationwide Friday sermon campaign was organized. Informative summaries, infographics, an FAQ page and a central repository to receive questions were developed. The CARD system was adapted to reduce vaccine-related anxiety. Accessibility barriers were reduced by disseminating vaccine appointment information while promoting mosques as vaccination sites during Ramadan and beyond. Materials were disseminated via a website, up to 6 social media platforms and emailed to over 400 mosques with a snowball strategy to maximize reach. Evaluation methods were limited due to resource limitations, but included positive qualitative feedback, active social media engagement, website traffic analytics, town hall polls showing improved confidence and uptake on government, public health and hospital websites across Canada.

Conclusion: Various interventions were utilized to promote COVID-19 vaccine confidence within this diverse, high-risk group. Intersectoral collaborations between health experts, faith leaders and grassroots organizations were critical for holistic community buy-in. Future vaccination campaigns should consider
employing a similar multipronged knowledge synthesis and dissemination strategy to maximize reach and impact. 

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Sex differential in survival: does it exist in a Canadian cystic fibrosis cohort?

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Introduction: A survival disadvantage for females with cystic fibrosis (CF) compared to males has been reported globally for decades. The factors contributing to the survival disparity are not fully understood. Some contemporary studies challenge if a sex gap still exists, as overall CF survival has significantly increased with advances in care. Our objectives were to determine if a survival difference between the sexes exists across the age spectrum in a contemporary cohort of Canadians living with CF and to identify factors that contribute to the sex gap.

Methods: We conducted a population-based cohort study using Canadian CF registry (CCFR) data, evaluating survival trends and patient characteristics between 2000 and 2016 inclusive. Conditional survival estimates by sex were calculated using the Kaplan-Meier method for the composite endpoint of death or transplant. Multivariable analyses were evaluated by Cox Proportional Hazards model to compare survival between males and females adjusted for known factors associated with survival. Changepoint analyses were conducted by using a segmented regression analysis, and the slope before and after the changepoint were estimated using linear regression with an interaction between sex and the time since the changepoint. Association between sex and clinical comorbidities was assessed using generalized linear mixed models.

Results: Between 2000 and 2016 inclusive, there were 5,618 patients followed in the CCFR, with 2,629 (46.8%) females and 2,989 (53.2%) males. There were 823 deaths, with significantly more deaths in females compared to males, 432 (16.4%) and 391 (13.1%) respectively (p=<0.001). Median age of survival was 39.5 years (95% CI: 37.9-41.5) in males compared to 34.8 years (95% CI: 33.4-36.3) in females. The gap in median age of survival between males and females started to decrease after age 20 years. At younger ages, the conditional median age of survival increased at similar rates between sexes, but after age 20 years, female conditional survival improved at a faster rate compared to males (1.01 versus 0.67 years/age respectively, p<0.001; Figure 1). Overall, females had a 25% increased risk of death or transplant compared to males (95% CI 1.09-1.43, p=0.004); however, this was attenuated after adjusting for confounders (HR 1.1, 95% CI 0.95-1.3, p=0.16). Further, females were more likely to experience CF-related diabetes (p=0.01), pulmonary exacerbations (p<0.001), Burkholderia cepacia complex or Pseudomonas aeruginosa (p=0.002) and low body mass index (p<0.001), which were all independently associated with worse survival.

Conclusion: Improved survival in females conditioning on older ages may be explained by a survival bias with the older female population representing a healthier cohort. A sex gap was identified, however, this
difference was explained by the fact that females were more likely to experience comorbidities that are known to increase the risk of death or transplant such as pulmonary exacerbations and diabetes.

**Acknowledgements:** Cystic Fibrosis Canada. Individuals living with CF and their families who have consented to having their data collected in CF patient registries. CF clinic staff who input data into the registry. Division of Respirology, Department of Medicine, University of Toronto.

Figure 1: Conditional survival for CF patients followed between 2000-2016 by sex using composite endpoint (death or transplant).
Abstract #28

Pre-Motor Cholinergic Circuitry Controlling the Upper Airway Musculature In-Vivo

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Introduction: The hypoglossal motor nucleus (HMN) innervates the tongue musculature and helps maintain an open upper airway for effective breathing. We previously identified that increased acetylcholine at the HMN suppresses tongue motor activity via an inhibitory muscarinic receptor mechanism that dominates nicotinic excitation (Liu et al., J Physiol, 565:965-80, 2005). We also identified that muscarinic receptor inhibition at the HMN strongly suppresses tongue motor activity during rapid-eye-movement (REM) sleep (Grace et al., Am J Resp Crit Care Med, 187:311-9, 2013). It is not known if cholinergic neurons in the intermediate reticular region of the medulla (pre-HMNIRt) modulate the HMN and tongue motor activity.

Methods: To identify pre-motor cholinergic circuitry controlling the upper airway musculature in-vivo, we applied a protocol (Aggarwal et al., Sci Rep, 10:550, 2020) to optically stimulate light-sensitive cation channels (channelrhodopsin, ChR2) expressed exclusively on cholinergic neurons in transgenic mice (ChAT-ChR2(H134R)-EYFP). Photo-stimulations consisted of 0-20mW, 10Hz, 2sec durations of 473nm light pulses. Tongue motor output was measured in response to photo-stimulations delivered from an optical fibre positioned 0.5mm above the HMN and pre-HMNIRt during isoflurane-induced anesthesia.

Results: In C57BL/6 mice (n=13) we first identified the stereotaxic coordinates of the pre-HMNIRt using microdialysis perfusion of potassium permanganate as 7.23±0.05 posterior, 0.9mm lateral and 6.21±0.05 ventral to bregma. Photo-stimulations delivered to the HMN and pre-HMNIRt elicited a power-dependent increase in tongue motor output, with threshold responses at 5mW at the HMN and 10mW at the pre-HMNIRt (P<0.05 vs. respective 0mW controls, n=15). Stimulations at the HMN elicited significantly larger responses compared to pre-HMNIRt (e.g., 374±25mV vs. 106±12mV at 20mW, P<0.001, n=15) within the same mice.

Conclusion: The findings indicate functional connections of cholinergic pre-HMNIRt neurons to the HMN. The reduced motor responses to the same intensity of stimulation at the pre-HMNIRt vs. the HMN may reflect net inhibitory influences from the pre-HMNIRt and/or recruitment of a smaller population of photo-activated neurons compared to the HMN. Experimental distinction between these explanations will be made via simultaneous pharmacological manipulations at the HMN coupled with anatomical identification of cholinergic neurons and their projections. Overall, these findings help identify the motor circuitry underpinning control of upper airway motor activity relevant to obstructive sleep apnea pathophysiology.

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Abstract #29

Barriers and Enablers to Objective Testing for Asthma and COPD in Primary Care: A Systematic Review Using the Theoretical Domains Framework

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Introduction: Although guidelines have long recommended objective pulmonary function testing to diagnose asthma and chronic obstructive lung disease (COPD), many patients in primary care receive a clinical diagnosis of asthma or COPD without objective testing. This often leads to unnecessary treatment with associated incremental costs and side-effects and delays actual diagnosis. We sought to systematically review and synthesize the barriers and enablers to lung function testing for asthma and/or COPD in primary care, with the aim of informing an intervention to bridge this care gap.

Methods: We searched the published literature for qualitative, quantitative, and mixed-methods studies reporting barriers and/or enablers to either in-office or out-of-office lung function testing for diagnosing asthma and/or COPD, in primary care. Two reviewers independently screened abstracts and full text articles; assessed methodological quality using the Mixed Methods Appraisal Tool; and extracted data from included studies. Identified barriers and enablers were categorized using the Theoretical Domains Framework (TDF), applying a pre-established coding manual.

Results: A total of 7988 unique articles were identified, 336 full-text articles were reviewed, and 18 studies are included in this systematic review. Of these 18, 12 were quantitative (eight had an MMAT score of 5/5, four had a score of 3/5), 3 were qualitative (two scored 4/5, one scored 1/5 on the MMAT but did not introduce any unique barriers/enablers), and 3 used mixed methods (all had an MMAT score of 5/5). All 18 addressed in-office testing and 11 also addressed out-of-office testing. Barriers and enablers overlapped for asthma and COPD, and in- and out-of-office settings. We identified more reported barriers than enablers, with barriers mapping to these 9 (of a possible 14) TDF domains (for both in- and out-of-office settings): Knowledge; Skills; Reinforcement; Social/professional role and identity; Beliefs about consequences; Memory, attention and decision processes; Intentions; Social Influences; Environmental context and resources. Enablers mapped to three domains (Intentions; Memory, attention and decision processes; Social influences) for in-office testing and five domains (Skills; Intentions; Memory, attention and decision processes; Environmental context and resources; Social influences) for out-of-office testing.

Conclusion: Barriers to objective testing for airways disease in primary care are complex and span many theoretical domains. Correspondingly, a successful intervention must leverage multiple behaviour change techniques. A theory-based, multifaceted intervention to address underuse of diagnostic testing for asthma or COPD should now be developed and tested.
Abstract #30

Developing a Decision Aid for a New Asthma Treatment Paradigm: Results from a Rapid-Cycle Design Study

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Introduction: Although daily inhaled corticosteroids (ICS) with an as-needed reliever has been the standard of care for mild asthma for decades, adherence to ICS is poor. Four seminal trials have shown that as-needed budesonide-formoterol is equivalent to daily ICS for prevention of severe asthma exacerbations. This new approach reduces ICS exposure and may address both intentional and non-intentional drivers of ICS non-adherence, but comes at the cost of slightly increased asthma symptoms. Given these pros and cons, clinicians and patients require guidance in reaching a preference-based treatment choice. Accordingly, we aimed to develop a mild asthma treatment decision aid (DA) while identifying and integrating patient and provider preferences.

Methods: We developed a prototype DA comparing first-line mild asthma treatment choices, comparing patient-relevant outcomes, side-effects, and costs. Comparative effect sizes were calculated through meta-analysis of high-quality randomized controlled trials. After face validation, we employed a rapid-cycle design process, whereby the DA was adapted according to pre-set criteria for “critical” and “emerging” issues after each “cycle” of user feedback. Each cycle consisted of a focus group with asthma patients aged ≥16 years and an interview with a primary care physician. This process continued until no new critical issues emerged. After the last round, a summative qualitative analysis of focus group/interview scripts was conducted to identify user preferences for such a tool.

Results: Through five rapid-cycle rounds, we recruited 21 patients (12/21 women; 10/21 aged ≥60 years; 12/21 holding a University degree) and five primary care physicians (2 community-based; 3 academic). Qualitative analysis identified three main thematic areas: tool content, format, and delivery process. In Content Preferences, users stressed the importance of using lay terms, availability in multiple languages, and a widely accessible reading level. Format Preferences included minimizing text content, using images, and minimizing tool length. Regarding Process Preferences, patients and clinicians acknowledged a need for interaction during the clinical visit to reach a final therapeutic decision and recommended complementing the DA with a single-page point-of-care conversation aid.

Conclusion: We integrated asthma patient and provider preferences in the development of a patient DA and point-of-care conversation aid to guide the treatment decision in mild asthma. User preferences for the content, format, and delivery of such a tool offer insights for decision aids across chronic diseases. This tool must now be integrated into primary care workflows to enable uptake and measurement of its impact on real-world decision-making and outcomes.
Abstract #31

The Impact of Chronic Rhinosinusitis on the Health-Related Quality of Life among Adult Patients with Cystic Fibrosis

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Introduction: Chronic rhinosinusitis (CRS) is a common co-morbidity among cystic fibrosis (CF) patients. Our objectives were to 1) estimate the prevalence of CRS with a large series of CF patients at the Toronto Adult Cystic Fibrosis Centre, 2) evaluate the impact of CRS on HRQoL of adults with CF and 3) compare CRS-specific, CF-specific and general HRQoL instruments in CF patients with CRS.

Methods: Consecutive CF patients from the Toronto Adult Cystic Fibrosis Centre were recruited in this cross-sectional study between March 2018 and January 2020. Demographic and clinical characteristics were collected. Participants completed the 22-Item Nasal Outcome Test (SNOT-22), Cystic Fibrosis Questionnaire-Revised for adolescents and adults over 14 years of age (CFQ-R), Cystic Fibrosis Quality of Life Evaluative Self-administered Test (CF-QUEST) and the 36-Item Short Form Survey (SF-36). Demographic and clinical characteristics were collected from the Toronto CF database. Diagnosis of CRS was made based on Canadian Clinical Practice Guidelines of CRS. The CRS proportion and 95% confidence interval (CI) was calculated using the Clopper-Pearson method. Continuous variables are summarized as median and range. Categorical variables are summarized as frequency and proportion. Associations between demographic variables and CRS were analyzed using the Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. QoL domains were correlated using Pearson’s correlation coefficient. All analyses were done using the open-source software R version 4.0.3.

Results: Out of 234 patients, 218 patients (93.2%) completed the questionnaires. The prevalence of CRS was 42.6% (95% CI: 35.5-49.8%). Demographic and CF-specific clinical factors were comparable between the CRS and non-CRS groups. CF patients with CRS reported higher SNOT-22 total, nasal, ear/facial pain and sleep scores, which exceeded minimal clinically important difference in all instances, indicating lower HRQoL. Patients with CRS also reported significantly lower respiratory domain of CFQ-R and physical health domains of CF-QUEST and SF-36. The physical (rho=-0.63) and mental (rho=-0.66) domains of SF-36 and CF-QUEST (rho=-0.76) had a strong correlation with SNOT-22.

Conclusion: CRS is a prevalent amongst CF patients. CRS significantly reduces HRQoL as shown in the CRS-specific, CF-specific and general HRQoL instruments, especially in the physical health domain. SNOT-22, CFQ-R, CF-QUEST and SF-36 show strong correlation with one another. CRS should be recognized, diagnosed and managed appropriately among CF patients, as CRS can adversely affect HRQoL.
Abstract #32

Assessing Obstructive Sleep Apnea Severity Through Application of Upper Airway Negative Pressure During Wakefulness.

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Introduction: Obstructive sleep apnea (OSA) is a common sleep disorder that remains underdiagnosed due to limited access to in-laboratory overnight polysomnography (PSG) and overnight home testing. A rapid test to quantify OSA severity, which can be administered to awake subjects, has the potential to dramatically increase the OSA diagnostic rate. Assessing upper airway (UA) collapsibility during wakefulness might be one means of accomplishing this. We therefore hypothesized that the degree of UA collapsibility, assessed by quantifying flow limitation in response to negative pressure (NP) applied via the mouth, would correlate with OSA severity as assessed by the apnea-hypopnea index (AHI).

Methods: Male and female subjects who had undergone clinically indicated PSG to determine their AHI were recruited. Over a 5-minute period, subjects were twice exposed to -3 cm H2O orally, which was applied automatically at the onset of expiration and terminated after five full breaths. The volume of subjects’ last 2 full breaths during NP application were compared with baseline breathing volume defined the 2 full breaths prior to NP exposure. The ratio of each subject’s breathing volume during NP exposure to the subject’s baseline breathing volume was deemed the NP ratio and represented the extent of flow limitation during NP application. The lower the ratio, the greater the degree of flow limitation.

Results: Thirteen subjects completed the study. NP ratios were inversely and exponentially related to the AHI (R = 0.80, P = 0.02). While the median NP ratio was not significantly different in patients with an AHI ³ 10 (i.e., OSA) versus patients with an AHI < 10 (i.e., without OSA) (0.840 [IQR = 0.118525] versus 1.112 [IQR = 0.3130625], p=0.07), the NP ratio was significantly lower in subjects with an AHI ³ 15 versus subjects with an AHI <15 (0.799 [IQR = 0.0799] versus 0.989 [IQR = 0.3402375], p=0.02).

Conclusion: NP ratio used as an index of flow limitation and UA collapsibility is strongly related to OSA severity (i.e., AHI). It also differentiated between subjects with an AHI of ³15 and those with an AHI < 15. These data suggest that the NP ratio may be a rapid and convenient means of quantifying UA collapsibility during wakefulness and of predicting the AHI. If so, testing for individuals’ NP ratios could markedly increase the rate of OSA diagnosis.

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Abstract #33

An automated machine learning classifier to predict prognosis in acute exacerbations of chronic obstructive pulmonary disease

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Introduction: Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a leading cause of hospitalization with a poor prognosis. While there exist prediction scores of prognosis in patients hospitalized with COPD exacerbations, many require the added step of entering input into an online calculator, which may be a barrier to use in busy clinical settings. Machine learning is a promising, emerging methodology that is particularly well-suited to take advantage of the rich, real world data available in electronic medical records (EMR). Its use in risk stratification of COPD exacerbations at time of hospitalization is limited. Our objective was to use machine learning to predict whether a patient hospitalized for COPD exacerbation is at increased risk for in-hospital death or need for intensive care at time of admission using only variables readily extractible from an average hospital EMR.

Methods: We used retrospective cohort data from two academic hospitals in Toronto, Canada between December 2011 and December 2018. We included patients with a primary admitting diagnosis of COPD. Those with a primary diagnosis of asthma, pneumonia, influenza or other respiratory disease were excluded. We selected variables available within 24 hours of emergency room presentation that were potential independent predictors of our outcome of interest, in-hospital death or need for ICU admission. Logistic regression was selected a priori as the machine learning classifier of choice. The sci-kit learn Logistic Regression classifier was fit and evaluated using k-fold cross validation with 10 folds.

Results: There were 2,030 hospital admissions with a primary admitting diagnosis of COPD. Through forward selection, we identified age, leukocyte count, serum bicarbonate level, partial pressure of carbon dioxide, and whether or not an arterial blood gas was ordered as variables to be included in the model. The mean area under the receiver operating characteristic curve was 0.78 with a standard deviation of 0.06 (fig. 1). The overall accuracy of the classifier was 89.6% with a positive predictive value of the outcome of 68.7%.

Conclusion: Our machine learning classifier may be a helpful tool to aid clinicians in making accurate prognostication of in-hospital death or need for ICU admission in patients within the first 24 hours of arriving at the hospital with an acute exacerbation of COPD. Because the variables are extractible from an average hospital EMR, it can be used to automatically present its predictions to clinicians without burden or delay.
Abstract #34

Pediatric acute asthma burden was reduced during the covid-19 pandemic lockdown; a single site experience.

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Introduction: Asthma is a chronic lung condition that is prone to exacerbation with viral triggers, and was identified as a possible risk factor for severe COVID-19 disease. Public health restrictions during the pandemic were intended to reduce viral spread for COVID-19, and indirectly have impacted circulating viruses. This study assessed the impact of the COVID-19 pandemic on paediatric asthma exacerbations. We hypothesized that frequency of visits would decline and severity would increase due to impaired primary prevention and delayed presentation to care.

Methods: This was a retrospective study comparing presentations for acute asthma to a tertiary care children’s hospital during the COVID-19 pandemic, from July 1 to December 31, 2020 to the same periods from 2018 and 2019. We assessed frequency of access and severity of presentation. Data was subjected to Chi-square and t-test analysis.

Results: Our study included 1753 acute asthma visits. There was an 80% reduction in acute asthma visits during the pandemic, compared with control years, versus a 38% reduction in all-cause acute care visits over the same periods. For asthma visits, there was no significant increase in acuity (CTAS 2.42 vs. 2.39; p=0.636), length of stay (16.7h vs. 17.6h, p=0.755), rate of admission (16.3% vs. 17.1% p=0.788), or rate of ICU admission (3.37% vs. 2.61%; p=0.545). In the subgroup of admitted patients, there was no statistically significant increase in length of stay (79.2h vs. 77.5h, p=0.888).

Conclusion: Public health measures appear to have had a specific protective effect on acute asthma with reduced acute care utilization relative to the reduction in all-cause presentations, without an increase in acute asthma presentation severity.
Abstract #35

Pulmonary macrophage subsets associated with lung allograft dysfunction revealed by single-cell RNA sequencing


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Introduction: Lung transplant (LT) recipients experience a low survival rate compared with other solid organ transplant recipients mainly due to chronic lung allograft dysfunction (CLAD). Acute lung allograft dysfunction (ALAD) episodes represent a risk factor of subsequent CLAD. The contribution of lung macrophages (Macs) to ALAD and CLAD is not clear. We applied single-cell RNA sequencing (scRNAseq) to profile allograft-derived cells during quiescence, ALAD, and CLAD, in order to determine the role of Macs in dysfunctional lung allografts.

Methods: Fresh bronchoalveolar lavage (BAL) cells from 6 LT patients, 3 with stable lung function (SLF) and 3 undergoing an episode of ALAD, as well as cells from 3 explanted CLAD lungs were used for scRNAseq. R Bioconductor and Seurat were used to perform QC, dimensionality reduction and visualisation, annotation, pathway analysis, and trajectory. Donor and recipient deconvolution was performed using single nucleotide variations.

Results: Our data revealed that Macs are highly heterogeneous (~12 transcriptionally distinct subsets that represented in all 3 SLF). We identified four Mac subsets more prominent in ALAD BAL compared to stable (Fig 1A). Of the four, three populations were uniquely present in the CLAD lung samples compared to a control donor lung sample (Fig 1B). Based on pathway analysis (not shown) and the top differentially expressed genes in BAL (Fig 1C) and CLAD lung (Fig 1D) samples, we annotated them as proinflammatory (CXCL10+), Ig-regulated (FcγRIIb+), and metallothioneins-mediated inflammatory (MT) Macs. Pseudotime analysis suggested that CXCL10+ and FcγRIIb+ Macs represent an earlier stage of differentiation compared with other Macs (Fig 1E). Deconvolution demonstrated that donor Macs are lost with time post-transplant (Fig 1F) and absent from CLAD lungs (Fig 1G).

Conclusion: Using scRNAseq, we observed Mac heterogeneity and identified specific subsets of Macs that may be associated with allograft dysfunction. Further exploration with scRNAseq will shed light on LT immunobiology and the role of Macs in allograft injury and dysfunction.
Abstract #36

Validation of CD4+ CD57+ PD1+ T Cells in Bronchoalveolar Lavage as a Biomarker of Lung Allograft Dysfunction

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Introduction: Our analysis on serial bronchoalveolar lavage (BAL) cells obtained from 25 lung transplant recipients (LTRs) using cutting-edge mass cytometry (MC) technology revealed a strong association between the frequency of CD4+ CD57+ PD1+ cells and subsequent lung allograft dysfunction (LAD). Here we present validation of this cell subset as a biomarker of incident LAD in an additional 25 LTRs.

Methods: MC was performed using a panel of 37 heavy metal-tagged antibodies against surface markers and intracellular cytokines. This technique was applied to BAL cells from 50 consecutive LTRs at their 3-, 6- and 9-month post-transplant surveillance bronchoscopies. LTRs were randomly assigned into two groups (Fig 1A). Semi-supervised identification algorithm on the first group of LTRs identified CD4+ CD57+ PD1+ cells as the highest discriminatory cluster between stable and LAD patients. We then tested best-fit threshold for frequency of the cell subset and applied it on the second group of LTRs for validation.

Results: Longitudinal analysis of the first randomized group of 25 LTRs demonstrated a higher frequency of CD4+ CD57+ PD1+ cells separating LAD (11.41±4.89%) from stable patients (4.43±2.11%; Fig 1B). Using a receiver operating characteristic curve, we identified a frequency of 7.8% as the best-fit threshold of the cell subset (Fig 1C). Survival analysis showed CD4+ CD57+ PD1+ T cells at 7.8% can discriminate stable from LAD patients in the first group of LTRs (Fig 1D). We then tested the performance of this threshold in the second group of LTRs. We found that in these additional 25 LTRs, those with BAL CD4+ CD57+ PD1+ cells above the threshold had a significantly lower freedom from incident LAD (p=0.05, Fig 1E).

Conclusion: Our data validated that emergence of CD4+ CD57+ PD1+ T cells precedes allograft dysfunction in a small cohort of LTRs. Further validation in larger cohorts, and molecular and functional studies on this cell population are underway and may lead to improved prediction of LAD and a better understanding of lung transplant immunobiology.
Abstract #37

Characterization and Relative Efficacy of Muscarinic Receptor Antagonism at the Hypoglossal Motor Nucleus to Block Inhibition of Tongue Motor Activity

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Introduction: Obstructive sleep apnea (OSA) is a common and serious breathing disorder caused by upper airway closure during sleep. The hypoglossal motor nucleus (HMN) is the source of motor output to the tongue musculature, with decreased motor activity in sleep precipitating OSA. We identified that muscarinic receptor antagonism at the HMN increases tongue motor activity in sleep, especially rapid-eye-movement sleep (Grace et al., AJRCCM, 187:311-9, 2013). A recent clinical study also showed that oxybutynin (a muscarinic receptor antagonist) in combination with atomoxetine (a norepinephrine reuptake inhibitor) greatly reduced OSA severity (Taranto-Montemurro et al., AJRCCM, 199:1267-76, 2019). However, it is unknown if oxybutynin can effectively block muscarinic-receptor inhibition at the HMN.

Methods: Adult rats were anesthetized with isoflurane and instrumented with electrodes to record tongue and diaphragm muscle activities. Microdialysis probes (220µm diameter, 1mm length) were inserted into the HMN for microperfusion of artificial cerebrospinal fluid (vehicle control) and selected muscarinic receptor agonists and antagonists.

Results: Compared to the baseline vehicle control, microperfusion of 100µM muscarine into the HMN resulted in a robust decrease in tongue motor activity (38±10%, p=0.002, n=8). Co-application of 100µM muscarine with 10µM atropine or 1mM scopolamine at the HMN effectively blocked this motor inhibition (2.5±8%, n=8 and 0±7%, n=10 respectively vs. baseline vehicle controls). However, unlike the powerful antagonism of muscarinic receptor inhibition at the HMN with atropine or scopolamine, persistent decreases in tongue motor activity occurred with 100µM muscarine despite microperfusion of 10µM or 100µM oxybutynin into the HMN (42±7%, p=0.002, n=7 and 33±6, p=0.002%, n=6 respectively). Likewise, persistent muscarine-induced decreases in tongue motor activity occurred despite microperfusion of 10µM, 100µM or 1mM omadacycline into the HMN (37±6%, P<0.001, n=10; 39±5%, p<0.001, n=10; and 24±7%, p=0.002, n=8 respectively).

Conclusion: It has been assumed that the major improvement in OSA severity with oxybutynin (and atomoxetine) in a recent clinical trial is due to blockade of cholinergic inhibition at the HMN. The results of the present study, however, indicate relatively weak muscarinic receptor antagonist properties of oxybutynin and omadacycline at the HMN compared to atropine or scopolamine, at least at comparative doses. Additional studies are ongoing to determine the relative efficacies of oxybutynin and omadacycline at the HMN to block hypoglossal motor inhibition in response to increases in endogenous acetylcholine (induced by the acetylcholine esterase inhibitor, eserine), and whether increases in oxybutynin and omadacycline concentrations at the HMN are necessary to elicit significant blocking effects.

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Abstract #38

Pulmonary Rehabilitation in Cystic Fibrosis Lung Transplant Candidates

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Introduction: Lung transplant (LTx) candidates with cystic fibrosis (CF) have ventilatory and musculoskeletal limitations contributing to reduced functional capacity. CF LTx candidates participate in pre-rehabilitation to improve their physical fitness, but perspective training response of CF related clinical factors has not been described. The aims of the study were to: 1) Characterize the muscle training volume response and six-minute walk distance (6MWD) in CF pre-LTx candidates with rehabilitation 2) Evaluate the determinants of pre-LTx 6MWD at baseline and with rehabilitation. We hypothesized that CF LTx candidates will have significant improvements in aerobic and muscle training volumes despite severe ventilatory limitations.

Methods: Single-center retrospective cohort study of CF LTx candidates with available pre-transplant exercise data between January 2010-May 2018. LTx candidates participated in supervised center-based rehabilitation 3 times/week until transplantation. Demographics, CF-related characteristics, and aerobic and muscle training volumes were abstracted from chart review. Paired t-tests were used to evaluate the change in 6MWD (start of program, 6 weeks, and every three-months) and weekly treadmill and muscle training volumes (lbs*repetitions*sets). Multivariable regression was used to evaluate the contribution of clinical co-variates on 6MWD pre-transplant.

Results: 86 CF LTx candidates (age 32±10 years, 49% males, BMI:19.6±2.8 kg/m2; FEV1: 23±5%, and listing 6MWD of 421±89 meters were evaluated. At listing, 88% required supplemental oxygen for exercise, 72% had ≥ 3 respiratory exacerbations in the prior year, and 37% were using non-invasive ventilatory (NIV) support at home. Median time on the transplant list was 87 days IQR [37-201]. With rehabilitation, there was a significant increase in treadmill speed of 0.6 mph (n=74, 95% CI (0.1-1.1), p=0.02) and in both the biceps [22.8 95% CI (10.9-34.8) lbs*repetitions] and the quadriceps training volumes [n=71, 18.8, 95% CI(10.6- 27.0) lbs*repetitions, p< 0.0001]. The 6MWD did not change pre-transplant [n=42, 1.2 m, 95%CI (-17.5 to 19.9), p=0.90]. Oxygen use [High (≥ 4L/min):Low O2: -84 95%CI (-143 to -25) meters and Low:No O2 -43 (-84 to -3) meters, p=0.01] and home NIV support (-57 95%CI (-96 to -19) meters, p=0.004) were associated with lower baseline 6MWD, whereas age, sex, BMI, FEV1, and respiratory exacerbation frequency were not significant. No clinical characteristics were associated with change in 6MWD pre-transplant.

Conclusion: CF LTx candidates demonstrated an increase in their exercise training volumes and had preservation of their exercise capacity with rehabilitation. Oxygen use and NIV support were important determinants of lower baseline exercise capacity, but were independent of exercise training response.

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Abstract #39

Evaluation of Physical Activity, Functional Capacity and Metabolic Risk Factors in Lung Transplant Recipients

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Introduction: Lung transplant (LTx) recipients have been observed to have reduced physical activity (PA) levels in the early post-transplant period (< 1 year) associated with decreased functional capacity and cardio-metabolic risk factors. The six-minute walk distance (6MWD) has been the most commonly used measure of functional capacity, but questionnaire-based estimates using the Duke Activity Status Index (DASI) have not been previously evaluated in the post-LTx period. The aims of this study were: 1) To characterize the relationship between PA levels and metabolic risk factors with self-reported functional capacity (DASI) 2) To evaluate the association of the DASI with traditional measures known to effect functional capacity.

Methods: Single center, cross-sectional analysis of 50 LTx recipients (> 6 months post-transplant) who completed a lifestyle survey on PA recruited from Jan/2020-Mar/2020. The survey assessed frequency and intensity of aerobic PA using an investigator developed questionnaire, along with DASI score. Demographics, clinical characteristics, metabolic risk factors, and 6MWD were ascertained through chart review. The associations between clinical, functional, and cardio-metabolic risk factors with the DASI were assessed using univariate and multivariable regression.

Results: LTx recipients [mean age: 57 ± 16 years, 66% males, BMI: 30.6 ± 17.8 kg/m2, and six-minute walk distance (6MWD): 62 ± 18 %] completed self-reported assessments (median time of 17 IQR (9-36) months post-LTx). 18 (36%) reported engaging in moderate-vigorous physical activity (MVPA ≥ 150 minutes per week as per guidelines). At the time of assessment, 68% participants had at least one of the following metabolic risk factors: hypertension (40%), hypercholesterolemia (36%), obesity (28%) and diabetes (18%). The DASI score (n=36) was 37 ± 19, representing the capacity for MVPA, with 6MWD differences in those reporting MVPA≥ 150 minutes/week versus MVPA < 150 minutes/week (545 ±120 versus 438 ±108 meters, p=0.01), with no difference in the DASI score (42 ± 17 versus 33 ± 19, p=0.18). With multivariable modelling, only 6MWD (11 points for every 100 meters, R2=0.58, p<0.0001) was independently associated with the DASI, independent of age, sex, and forced expiratory volume 1 second. The DASI was not associated with presence of metabolic risk factors, chronic allograft dysfunction or time-period (early or late ≥ 1 year) post-transplant.
Conclusion: The majority of LTx recipients reported decreased levels of participation in MVPA, associated with lower 6MWD but not DASI score. Further study is needed to evaluate whether the DASI can be applied as a self-reported functional capacity measure post-LTx.

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Abstract #40

Fibrotic interstitial lung disease survival in a national Canadian registry.

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Introduction: Fibrotic interstitial lung diseases (ILDs) are a group of progressive lung disorders with various etiologies. Their heterogeneity and relative rarity have been a significant barrier to research. The Canadian Registry for Pulmonary Fibrosis (CARE-PF) is a national, multicentre, prospective registry designed to study the natural history of ILD and is the largest of its type in the world. The aim of our study was to (1) describe the current real-world survival of fibrotic ILD in Canada and (2) describe the association between patient level characteristics and fibrotic ILD survival, using a large national ILD registry.

Methods: All adult patients with ILD prospectively registered in CARE-PF were included. Diagnoses included idiopathic pulmonary fibrosis (IPF), fibrotic hypersensitivity pneumonitis (HP), connective-tissue disease-related ILD (CTD-ILD), unclassifiable ILD and other ILD. Other ILD included non-IPF idiopathic interstitial pneumonias, sarcoidosis, and rarer ILD subtypes. Patients were censored at date of last follow-up, transplant or death. 1-, 3- and 5-year transplant-free survival was determined for the overall cohort and each ILD subtype. Cox proportional hazards modelling was used to evaluate associations between patient characteristics and transplant-free survival.

Results: 3756 patients with ILD were included. Baseline characteristics are shown in Table 1. During the study period, median patient follow-up was 3.95 (IQR 2.04-6.69) years. There were 777 deaths and 167 lung transplants. 1-, 3- and 5-year transplant-free survival was 96.7%, 85.0% and 69.5% respectively. Survival was lowest for IPF and highest for CTD and Other-ILD. Older age (HR 1.078, 95% CI 1.065-1.091, p<0.0001), oxygen use (HR 1.696, 95% CI 1.326-2.170, p<0.0001), and lower percent predicted FVC (HR 0.984, 95% CI 0.977-0.991, p<0.0001) and DLCO (HR 0.974, 95% CI 0.967-0.981, p<0.0001) were associated with higher risk of mortality on adjusted analysis. Interestingly, after adjusting for patient characteristics, there was no association seen between ILD subtype and mortality.

Conclusion: We describe the current real world survival for a large, national, prospective cohort of ILD. After adjusting for relevant patient characteristics, we found that ILD subtype was not associated with survival. These findings support the theory that some fibrotic ILDs share a unifying disease process and prognosis, regardless of the underlying cause.
Abstract #41

Glutamatergic pre-Bötzinger complex neurons as potential targets to alleviate opioid-induced respiratory depression

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Introduction: The opioid crisis in Canada takes thousands of lives a year with no end in sight. One of the main symptoms of overdose, and a major concern when using opioids, is a decrease in breathing known as respiratory depression. The pre-Bötzinger complex (preBötC) is a small region within the brainstem that has been shown to have a critical role in respiratory rhythm generation, particularly inspiration. Within the preBötC, there is a large population of glutamatergic neurons, with a subpopulation co-expressing µ-opioid receptors. When opioids bind to these µ-opioid receptors, glutamatergic activity is inhibited and opioid-induced respiratory depression (OIRD) occurs. Subsequently, blocking µ-opioid receptors in preBötC neurons restores breathing after OIRD. One marker of these neurons is vesicular glutamate transporter 2 (VGLUT2), which is involved in glutamate release. Therefore, targeting these VGLUT2 neurons is a potential method for modulating inspiration. The purpose of this project is to identify the activation of the preBötC as a viable method to prevent respiratory depression, and fatality, caused by opioid use. We hypothesis that chemogenetic activation of glutamatergic neurons within the preBötC will alleviate respiratory depression by fentanyl in mice.

Methods: Cre-lox recombination was used to virally insert designer receptors exclusively activated by designer drugs (DREADDs) into the preBötC of VGLUT2 cre+/+ mice. DREADDs were designed to be exclusively activated by clozapine-N-oxide (CNO). After 4 weeks for viral replication and expression, mice were anesthetized, and electrodes were attached below the diaphragm and within the genioglossus for monitoring of respiratory rates. Breathing was manipulated with injected fentanyl (5 µ/kg) and CNO (1 mg/kg), with saline as a control. Following the experiments, mice were perfused, and brains were collected for histology to confirm the localization of the virus injection in the preBötC.

Results: After administration of fentanyl, male mice displayed a significantly increased respiratory rate following DREADD activation compared to fentanyl alone, from minute 48 post-injection onwards. Control mice were given saline in place of fentanyl. Activation of DREADDs in control male mice increased respiratory rate compared to saline alone from minute 10 post-injection onwards. DREADD activation therefore led to increased respiratory rate. However, this increase occurred consecutively to OIRD, indicating that earlier CNO administration would be necessary to directly combat OIRD.

Conclusion: Chemogenetic activation of DREADDs seems promising for increasing respiratory rate. However, earlier CNO administration needs to be explored to maximize DREADD activation in the period directly following fentanyl administration.

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Abstract #42

Donor airway bile acid as a biomarker of aspiration and predictor of post-transplant outcomes

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Introduction: Emesis and aspiration in lung transplant donors contributes to donor lung damage and may promote post-transplant allograft dysfunction. Currently, the degree of aspiration at time of donor death is assessed solely by visual inspection via bronchoscopy. While this can identify gross macroaspiration, it does not detect more subtle aspiration of gastric contents which could result in chemical pneumonitis, contributing to lung damage. A previous small study by our group identified that aspirated total bile acids (TBA) in donor large airway bronchial wash (LABW) samples was associated with acceptability of donor lungs for transplant. Herein, we seek to validate this finding in a large retrospective cohort and assess the association between donor LABW TBA and recipient outcomes.

Methods: TBA was measured in LABW of 605 consecutive lung donors from 2012-2018 with available LABW samples at the Toronto Lung Transplant Program. TBA levels were compared in donor lungs deemed unsuitable for transplant (n=42), those requiring further assessment on ex vivo lung perfusion (EVLP) (n=213), and those suitable for direct transplantation (n=350). Associations between LABW TBA concentrations and performance of donor lungs on EVLP were assessed. The relationship between donor LABW TBA and post-transplant recipient outcomes were evaluated.

Results: Donor TBA was higher in lungs deemed unsuitable for transplant compared to those suitable for direct transplant (p<0.001) and those requiring further assessment on EVLP (p=0.04) (Figure 1). TBA concentration in donor LABW also correlated with average EVLP perfusate Ca2+ (r=0.251; p<0.001), pH (r=-0.234; p<0.001), HCO3 (r=-0.195; p<0.001), glucose (r=-0.189; p=0.01), lactate (r=0.215; p<0.001), IL-6 (r=0.261; p=0.01), IL-8 (r=0.161; p=0.03), and sTNFR1 (r=0.177; p=0.03). A TBA cut-off of 1250nM was able to differentiate declined donor lungs directly declined and those suitable for direct transplantation with a 90% specificity (AUROC: 72.6%). Based on this cut-off, a high donor TBA was associated with post-transplant recipient outcomes: longer time to extubation (HR=0.48 [95% CI=0.35-0.66]) and shorter time to death (HR=1.84 [95% CI=1.24-2.75]) (Figure 2).

Conclusion: In a large single-center retrospective cohort we observed that TBA measured in donor LABW was associated with suitability of donor lungs for transplant, performance of lungs on EVLP, and adverse recipient outcomes after lung-transplant. Triaging donor lungs using a high TBA cut-off may help better allocate the EVLP technology for donor lung evaluation and potential treatment of donor aspiration may help improve lung transplant outcomes.

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10-Fold Cross Validation ROC Curve

Mean AUROC ± SD = 0.78 ± 0.06
Abstract #43

Optogenetic activation of preBötzinger Complex cells alleviates respiratory depression by opioids

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Introduction: Opioids are extensively used for their analgesic properties but they can lead to respiratory depression. The analgesic effect of opioids is due to activation of µ-opioid receptors (MOR) in the central nervous system and no treatments are currently available to prevent respiratory depression without reducing their analgesic properties. Neurons expressing tachykinin precursor 1 peptide (TAC1) located in the preBötzinger Complex (preBötC) also co-express neurokinin-1 receptors (NK1R) and MORs. NK1R neurons are preferentially inhibited by opioids and play an essential role in mediating opioid-induced respiratory depression. Here, we tested the hypothesis that optogenetic activation of TAC1-expressing preBötC cells will prevent or reverse respiratory rate depression by opioids.

Methods: Using a Cre-loxP recombination approach, we injected, in TAC1 Cre recombinase mice the adeno-associated virus containing the gene cassette of the excitatory channelrhodopsin-2 ChETA flanked between loxP sites. After a four weeks period to allow ChETA expression in targeted cells, a 200 µm optical fiber was positioned above the preBötC for laser stimulation with blue light (wavelength: 480 nm) and respiratory rate was measured in anesthetized mice. Once breathing was stable (>20 min), the clinically-relevant µ-opioid drug fentanyl (1mg/kg) was administered by intramuscular injection. About 5 min after fentanyl injection, targeted preBötC cells were stimulated using laser stimulations (frequency: 30Hz, duration of stimulation: 330ms).

Results: Data show that fentanyl depressed respiratory rate by about 40% in 5 minutes and stimulation of TAC1-expressing preBötC cells increased breathing rate back to baseline level when the laser was on; an effect that was reversible.

Conclusion: TAC1-expressing preBötC may constitute cell targets to prevent respiratory rate depression by opioids. These results may help identify the cells mediating respiratory depression by opioids, an essential step toward the development of therapeutic targets to reduce the risk of opioids overdose and associated mortality.

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Abstract #44

Idiopathic central sleep apnea in infants: an observational cohort study

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Introduction: Central sleep apnea (CSA) is characterized by recurrent apneas during sleep associated with oxygen desaturations and typically related to medical comorbidities such as prematurity or neurological conditions. However, term, healthy infants may also present with significant, unexplained CSA requiring respiratory support and monitoring for prolonged periods. To date, there is a paucity of literature describing idiopathic CSA, specifically investigations, interventions and clinical outcomes of these infants. Our aim was to describe the clinical manifestations, polysomnography (PSG) data, interventions and trajectory of CSA in healthy infants.

Methods: This is a retrospective study of infants with idiopathic CSA diagnosed on PSG between January 2011 to April 2021 at the Hospital for Sick Children, Toronto, Canada. Inclusion criteria included a central apnea-hypopnea index (CAHI) > 5 events/hour, minimum gestational age of 36 weeks, and absence of a medical diagnosis causing CSA. Descriptive statistics were used to examine patient demographics, PSG data and treatments provided. Initial and follow-up PSG data were compared using Wilcoxon pair signed-rank tests. This study was approved by the SickKids Research Ethics Board.

Results: Eighteen infants (male, 77.8%) diagnosed with CSA were included with median (interquartile range; IQR) gestational age of 38.0 (37.0-39.0) weeks. Presenting clinical features were apneas (n=18, 100%), frequent desaturations (n=18, 100%), hypercapnia (n=8, 44.4%) and bradycardia (n=3, 16.7%). Initial PSGs were completed at a median (IQR) age of 1.2 (0.6-1.6) months. The majority of infants had isolated CSA (61.1%) followed by CSA with co-existing obstructive sleep apnea (OSA) (27.8%), CSA and nocturnal hypoventilation (NH) (5.6%) and CSA, NH and OSA (5.6%). The majority of infants were prescribed oxygen supplementation (14; 77.8%) followed by caffeine (5; 27.8%) with one infant (5.6%) prescribed noninvasive ventilation. Thirteen (72.2%) infants had follow-up PSGs at a median (IQR) age of 12.1 (9.3-14.7) months. Compared to baseline diagnostic PSGs, at follow up there was a significant reduction in median (IQR) CAHI [27.1 (13.9-81.6) vs 4.7 (2.7-8.0) events/hour respectively; p=0.001], desaturation index (DSI) [33.0 (9.6-88.1) vs 6.3 (3.1-14.4) events/hour respectively; p=0.002], arousal index [14.8 (10.1-18.7) vs 8.7 (5.9-11.1) events/hour; p=0.028] respectively; average transcutaneous carbon dioxide [44.0 (40.2-47.4) vs 38.3 (35.3-41.9) mmHg respectively; p=0.025] and an improvement in nadir oxygen saturation [77.6 (67.5-83.3) vs 84.0 (81.0-87.5)% respectively; p=0.033].

Conclusion: Infants with significant unexplained CSA at birth requiring respiratory support have a favourable clinical trajectory over time. Further research is needed to understand the etiology of this rare disorder.
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Abstract #45

Contemporary Birth Rates of Cystic Fibrosis in Canada

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Introduction: Cystic fibrosis (CF) birth prevalence in Canada is historically estimated to be 1:3600 live births. However, contemporary incidence of CF may differ due to longer median survival of CF patients, widespread implementation of newborn screening (NBS) programs, improved genetic counselling and pre-implantation genetic testing, immigration and population mixing, and recognition of milder clinical phenotypes resulting in adult-diagnoses of CF. As such, it is important to re-examine CF birth prevalence in order to provide people with accurate estimates of the risk of having a child with CF today. Our objectives were to estimate the current CF birth rate in Canada with adjustments for delayed diagnosis and the impact of NBS.

Methods: This population-based cohort study utilized data from the Canadian CF Registry (CCFR) and Statistics Canada to evaluate CF incidence in Canada between 1995-2019. The CCFR captures demographic and clinical data on all CF patients followed at the 42 accredited CF clinics across the country. It is estimated that <1% of patients decline consent to participate in the registry. The number of live births by year, sex, and province during the study period were calculated. Poisson regression, with the number of live births used as an offset term, was used to estimate the CF birth incidence overall, by province, and gender, both over the study period and by year. Incidence rates were reported using the observed data, and also adjusted through simulation accounting for the effect of delayed diagnoses in the latter years of the population cohort.

Results: During the period 1995-2019, the incidence of CF is 1:3566 (95% CI: 1:3430, 1:3708) live births in Canada. The incidence rate for males was 1:3522 (95% CI: 1:3337, 1:3717) and females was 1:3610 (95% CI: 1:3413, 1:3818). The incidence by province varied, with CF being most common in Quebec (incidence of 1:2927), followed by Atlantic provinces (1:2849), Western provinces (1:3847) and Ontario (1:3919). In each province, the majority of CF diagnoses were in Caucasians (84.4%-96.0%), with homozygous F508del being the most common mutation combination (43.6%-60.2%). Canadian CF incidence rate has decreased by 1.02% per year (p<0.0001). Using historical data to account for delayed diagnoses, the overall Canadian incidence estimate of CF is 1:2519 live births. Further adjustments also taking into consideration implementation of NBS, the incidence of CF would then be 1:3076.

Conclusion: Considering the impact of delayed diagnoses and the introduction of NBS allow a more accurate estimate of CF birth rates, and indicates that the incidence of CF may be more common than currently is reported. Further, the incidence of CF in Canada is decreasing over time and further study is needed to understand the contributing factors.
Abstract #46

Non HLA Antibodies In Serum Prior To The Onset Of Chronic Lung Allograft Dysfunction

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Introduction: Non-human leukocyte antigen (HLA) antibodies have been associated with chronic lung allograft dysfunction (CLAD). Whether they predate CLAD is unclear. We hypothesized that patients destined to develop CLAD might develop non-HLA antibodies prior to CLAD onset.

Methods: In a single centre retrospective study, we examined 100 consecutive crossmatch negative recipients of a bilateral lung transplant between 1 January 2013 and 31 December 2014. Using a two-colour fluorescent antigen microarray with 152 unique antigens, we measured IgM autoantibodies in pre-transplant and six months post-transplant serum samples. Log-transformed mean fluorescent intensities (MFIs) were determined for each antigen. CLAD was determined using published definitions. Significance analysis of microarrays (SAM) was used to analyze differences in antigen reactivity with a false discovery rate of 0.05. Paired and unpaired analyses were used to examine differences within and between recipients who developed CLAD within 5 years and recipients who remained CLAD free at 5 years post-transplant.

Results: Serum samples were available for 96 recipients - 35 (36.5%) developed CLAD and 61 remained CLAD-free within 5 years. Total IgM and IgG reactivity decreased in most patients post-transplant (Fig 1A), although IgM levels were stable in patients developing CLAD. Three IgM autoantibodies - including anti-club cell secretory protein (CCSP, Fig 1B) - increased in most patients post-transplant; this increase was of greater magnitude in patients later developing CLAD. Patients destined to develop CLAD also had an increase in IgG fluorescence directed at human core histones (Fig 1C).

Conclusion: Our results suggest that there may be important differences in non-HLA antibody reactivity that appear before the onset of CLAD. These observations, which require validation in further studies, may also indicate a specific role for non-HLA antibodies directed at club cell secretory protein and nuclear antigens in CLAD development.

Acknowledgements: Dr. Stephen Juvet and Dr. Tereza Martinu.
Abstract #47

Oscillometry Tracks Graft Injury Following Lung Transplant: Association With Acute Cellular Rejection And Chronic Lung Allograft Dysfunction (CLAD)

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Introduction: CLAD is the major cause of death after lung transplant (LTx). Among the multiple factors contributing to the CLAD development, acute rejection (AR) is the most significant. To allow for earlier identification and treatment of AR, patients are routinely monitored with spirometry. Our group previously reported that oscillometry (Osc), specifically its metrics of small airway obstruction and ventilatory inhomogeneity (AX, X5 and R5-19), is more sensitive than spirometry in detecting AR-associated graft injury and improvement after treatment. Hypothesis: Osc tracks graft injury associated with AR and predicts risk of CLAD.

Methods: This prospective study enrolled 289 bilateral lung recipients between Dec 2017 and Mar 2020 for Osc prior to every clinically indicated spirometry. Of these, 234 patients had follow-up of ≥3 months, while 177 ≥ 6 months, of whom 39 developed CLAD. Nine CLAD patients were excluded from analysis due to insufficient Osc measurements at time of CLAD-onset. Patient demographics, primary diagnosis, CMV match-status, HLA status and transbronchial biopsy A-score, a cumulative index of biopsy-proven ARs were extracted from the Toronto Lung Transplant Database. Multiple regression models were performed to investigate the relationship between variance in oscillometry parameters and A-score. Cox regression was used to assess the association of Osc with risk of developing CLAD, factoring in age, sex, relevant clinical variables, the initial, baseline (defined as the average of 2 best achieved post-LTx) and intra-subject variance of AX, X5 and R5-19.

Results: Multiple regression models showed that A-score was positively associated with the variance in Osc parameters. Cox analysis in 168 patients with ≥ 6 months follow-up found higher A-scores to increase the risk of CLAD (HR=1.62, p<0.05). A higher variance in R5-19, AX and X5 was associated with increased risk of CLAD (HR=1.28, 1.29 and 1.50 respectively, p<0.05), while variance in %FEV1 was not associated. Lastly, the analysis showed that the initial R5-19 and AX (HR=1.37 and HR=1.32 respectively, p<0.05) post-LTx were associated with the risk of CLAD.

Conclusion: Osc metrics of lung function reflect graft injury that is associated with AR. Intra-subject variance in Osc measurements is a marker of ongoing graft injury, which is reflected in the association with the A-score and the observed increased hazard risk of CLAD. Furthermore, the initial Osc measurements are associated with risk for CLAD. As such, post-LTx graft monitoring with Osc provides a risk assessment of subsequent CLAD with the potential for improve early detection of CLAD. This suggests that Osc should be used as a routine method for graft monitoring post-lung transplant.
Abstract #48

Investigating for laterality defects in primary ciliary dyskinesia

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Introduction: In Primary Ciliary Dyskinesia (PCD), organ laterality defects are common, ranging from situs inversus totalis (SIT) to situs ambiguous (SA). SA may include cardiac, intestinal, and splenic anomalies, yet targeted imaging of these organs is not universally recommended in PCD consensus statements. Without imaging beyond standard chest radiography (CXR), these clinically significant anomalies may go undetected. We hypothesize that in PCD patients clinically significant SA anomalies remain undetected on standard CXR and are more prevalent on targeted investigations such as ECHO, ultrasound and computed tomography.

Methods: This cross-sectional observational study collected data from PCD clinics at two Canadian Children’s Hospitals from 2012-2020. Participants <30 years old with a confirmed (2 pathogenic variants in one PCD gene or classic ciliary ultrastructural defect) or clinical (compatible phenotype with two low nasal nitric oxide levels or PCD family history) diagnosis of PCD were enrolled. CXR reports were reviewed by 1 of 2 physicians, and reports of other scans, including chest CT, abdominal ultrasound (AUS), echocardiogram, upper gastrointestinal series (UGI), and nuclear splenic scans (or blood smear), were extracted from records.

Results: 159 PCD patients were included, with a mean diagnostic age of 6.3 years (52% male). From CXR images alone, 90 (56%) had SS, 59 (37%) had SIT, and 10 (6%) had SA. Additional clinically indicated imaging included echocardiogram (42, 47%), AUS (72, 45%), chest CT (118, 74%), and UGI (27, 17%). These targeted investigations detected significant laterality defects not apparent on CXR alone and more than doubled the SA prevalence (30, 19%). Identified SA anomalies were cardiac (16, 10%), intestinal (4, 3%), and/or splenic architectural anomalies (13, 8%) (Table). Splenic function, assessed with peripheral blood-smear (30, 19%) and/or scintigraphy (8, 5%), revealed two (1.3%) patients with functional asplenia and polysplenia, and one further complicated by splenic sequestration and infarct. Both patients required prophylactic antibiotics. An additional 10-month-old infant (CCDC40-/-) with SIT and polysplenia died from Streptococcus pneumoniae sepsis, with presumed abnormal splenic function.

Conclusion: Some clinically significant SA defects are not detectable on CXR, and targeted thoracoabdominal imaging is warranted in PCD patients. Splenic architectural defects may result in splenic
dysfunction, pre-disposing PCD patients to sepsis and even death if not promptly placed on antibiotic prophylaxis and accelerated vaccination protocols. We propose that AUS and echocardiograms be routinely performed in all PCD patients, and those with splenic architectural anomalies should have functional splenic assessments.

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Abstract #49

Association between neonatal hospital length of stay and lung function in children with Primary Ciliary Dyskinesia: A multi-center cohort study

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Introduction: To evaluate the association between neonatal hospital length of stay and supplemental oxygen duration with lung function in children with PCD, independent of genotype or electron microscopy confirmed ciliary ultrastructural defect (EM-defect). We hypothesize that longer neonatal hospital length of stay and supplemental oxygen duration are associated with worse lung function.

Methods: Our study utilized data from a ‘Genetic Disorders of Mucociliary Clearance Consortium’ prospective longitudinal multi-center cohort study. Participants were enrolled from 2006 to 2011 and followed yearly for 5 years. At enrollment participants were <19 years old with a confirmed diagnosis of PCD. Participants with <2 visits were excluded. The exposure variables are neonatal hospital length of stay (neonatal-LOS) and supplemental oxygen duration in days since birth (SuppO2). Lung function, measured annually by spirometry, was defined as percent-predicted forced expiratory volume in one second (FEV1pp). A linear mixed effects model with repeated measures, random intercepts and adjusting for EM-defect was used. Genotype was collinear with EM-defect and excluded from the model. Sensitivity analyses were performed using different modelling approaches. Statistical significance defined as a two-tailed p-value<0.05. Analyses were completed using RStudio Team (2015).

Results: We included 123 participants with a total of 578 visits and median follow-up of 6 years (range 1-6 years). Participants were 47% male and the average enrollment age was 8.3 years. The median neonatal-LOS was 9 days (range 1-90) and median SuppO2 was 5 days (range 0-180). In the model, age (-0.74 FEV1pp per year (95%CI: -1.14 to -0.34), p<0.05) and neonatal-LOS (-0.27 FEV1pp per hospital day (95%CI: -0.53 to -0.01), p<0.05) were associated with worse lung function after adjusting for EM-defect. Model fit statistics and sensitivity analyses suggested that the original model was the best fit for the data.
Conclusion: We found that neonatal-LOS is significantly associated with worse lung function. Future research on the mechanisms and management of pediatric PCD among patients with neonatal hospitalizations may lead to improved lung health outcomes.

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Abstract #50

What Evidence Is Available On Glucocorticoid-Induced Myopathy In Asthma? A Systematic Review

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Introduction: Myopathy has been described as an adverse effect of glucocorticoids (GC) which can lead to considerable morbidity. The evidence on GC-induced myopathy in asthma has not been well described. To facilitate evidence-based practice, we aimed to review the evidence of GC-induced myopathy in people with asthma, and the underlying characteristics of GC (type, dosage, and duration) associated with myopathy.

Methods: A systematic review (PROSPERO CRD42020142448) was performed, with a search strategy using MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL databases. Studies were included if they comprised adults or adolescents with asthma, taking systemic GC, and measures of muscle impairments. Methodologic quality was evaluated using the National Heart, Lung, and Blood Institute Quality Assessment Tool.

Results: Nine studies met the eligibility criteria. Six studies focused on patients with GC-dependent asthma; three studies included patients with acute exacerbation requiring critical care admission for mechanical ventilation. The methodologic quality of most studies was fair or good (n=7). Two studies reported significantly lower inspiratory muscle function in outpatients with GC-dependent asthma taking oral GC daily (≥10mg), compared to those who were not on regular oral GC. Three studies did not find significant differences in respiratory or limb muscle function between the two groups. Studies on patients with asthma exacerbation taking GC intravenously reported 11-36% suffering from limb muscle weakness during or after their ICU stay. However, one study showed that only patients who were on both intravenous GC and neuromuscular blocking agents developed myopathy, but not those who were on only intravenous GC (41% vs 0%). Two studies with GC-dependent asthma reported significant associations between dosage of oral GC use and inspiratory and limb muscle function, whereas four studies did not find any significant correlations among the characteristics of oral GC and respiratory or limb muscle size or function.

Conclusion: There were inconsistent results from studies on GC-induced myopathy in people with asthma, and the association between type, dosage and duration of GC and myopathy. Future studies should use a commonly accepted operational definition of myopathy, utilize a cohort study design, measure the cumulative dosage of GC, and integrate possible confounding factors in the analysis.

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Abstract #51

Positional Therapy for the Treatment of Positional Obstructive Sleep Apnea in Children: A Pilot Study

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Introduction: Persistent obstructive sleep apnea (OSA) is highly prevalent and the gold standard therapy, continuous positive airway pressure, is limited by poor adherence. Recent Canadian data highlights that half of children with moderate to severe OSA have positional OSA, a phenotype characterized by the predominance of airway obstruction in supine position as measured by the obstructive apnea-hypopnea index (OAHI) on polysomnography (PSG). Positional device therapy treats OSA by preventing supine sleep but has not yet been studied in children. The primary aim of this study was to evaluate the efficacy of positional therapy for the treatment of positional OSA in a paediatric population.

Methods: In this observational cohort study, children aged 4-18 years deemed to have positional OSA with OAHI ≥ 5 events/hour on baseline PSG underwent a second PSG to evaluate the efficacy of a positional device. Descriptive statistics were used to examine patient demographics, anthropometrics, and PSG parameters. Changes in PSG data were compared using Wilcoxon signed rank tests. Research Ethics Board approval was obtained from The Hospital for Sick Children, Toronto, Canada.

Results: Ten children were included (8 male, median age 11.2 years, median body mass index z-score 1.6). PSG data obtained while using a positional device showed a significantly reduced median (interquartile range [IQR]) percentage of total sleep time in supine position compared with baseline (4.2 [1.1-25.2]% vs 54.4 [35.0-80.6]% respectively; p=0.002) and a significantly reduced OAHI using positional device therapy compared with baseline (6.7 [1.0-13.7] events/hour vs 15.2 [8.3-25.6] events/hour respectively; p=0.004). The improvement in OSA was primarily observed during non-rapid eye movement sleep using a positional device compared with baseline (5.3 [0.8-13.7] events/hour vs 11.1 [6.5-30.4] events/hour respectively; p=0.006). With regards to gas exchange parameters, there was significant reduction in the median (IQR) oxygen desaturation index using the positional device compared with baseline (5.7 [3.7-14.4] events/hour vs 10.7 [5.8-26.0] events/hour respectively; p=0.037).

Conclusion: To our knowledge, this is the first study to objectively investigate the use of positional device therapy during sleep for the management of OSA in children and demonstrate its effectiveness as a treatment for OSA. Positional therapy has the potential to change clinical practice as an effective, cost-efficient, and non-invasive treatment option for positional OSA.
Abstract #52

Mechanisms underlying opioid-induced respiratory depression and analgesia in larval zebrafish

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Introduction: Opioid drugs can produce both analgesia and lethal respiratory depression. Since 2016, over 19,000 Canadians have died of an opioid overdose. Mechanisms of opioid inhibition are not well understood and there is an urgent need to find safer pain therapies without the risk of respiratory depression. Therefore, we aimed to understand the respiratory and pain-relieving effects of opioids using novel zebrafish assays. Zebrafish are amendable animal models with an intact nervous system and high genetic homology to humans. Using these assays, we tested a variety of drugs including serotoninergic agonists, glutamatergic modulators, and calcium channel activators, for their ability to reverse opioid-induced respiratory depression.

Methods: We have established phenotype-based approaches using in-vivo zebrafish models of respiratory depression and analgesia by fentanyl. To quantify respiratory depression, we used mandible movements in 12-14 day post-fertilization (dpf) larvae as an index of respiratory activity. To quantify analgesia, we measured the escape swimming response to nociceptive stimuli such as formalin or AITC combined with fentanyl to induce analgesia. We then applied various candidate drugs to measure their effects on respiratory depression and analgesia.

Results: Respiratory rate was normalized to each fish’s baseline (baseline=100%). Zebrafish had differential sensitivity to opioids. The AB strain had significantly reduced respiratory rate in response to 1µM fentanyl (p<0.001), where the Tübingen (TU) strain and AB x TU crosses did not. In AB zebrafish, a dose-dependent decrease in respiratory rate was observed with 1µM and 3µM fentanyl (p<0.001). The opioid antagonist naloxone (20µM) reversed respiratory depression by fentanyl (p<0.001). Respiratory depression by 1µM fentanyl was reversed by the AMPA receptor positive allosteric modulator CX614 (5µM, p<0.001) but not the serotoninergic 5-HT4 agonist BIMU8 (10µM). Calcium channel activators nefiracetam (1µM) and FLIP-64176 (1µM) reversed respiratory depression by 3µM fentanyl (p=0.002 and p=0.001, respectively). Formalin (0.05%) and AITC (100µM) significantly increased swimming velocity (p<0.001, for both), an effect reduced by 3µM fentanyl (p=0.037 and p<0.001, respectively). CX614 reversed fentanyl analgesia when applied with formalin (p=0.007).

Conclusion: Our models show that respiratory depression and analgesia by opioids can be measured in 12-14 dpf larvae. Respiratory depression by fentanyl is reversed with AMPA allosteric modulators and calcium channel activators. Analgesia is also reversed with the former. Our novel zebrafish models can be used to investigate the mechanisms of opioid inhibition to better understand how to block respiratory depression while preserving analgesia.

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Abstract #53

Assessing Equity, Diversity and Inclusion in HHT Research

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Introduction & Objectives: Systemic barriers impair equal access to medical care and research, resulting in substantial health disparities among racialized communities. Non inclusive medical research can have numerous implications, ultimately reinforcing the exclusion of racialized populations within the medical system and continuing health outcome disparity. In an effort to promote equity, diversity, and inclusion (EDI) in Hereditary Hemorrhagic Telangiectasia (HHT) research, we aim to identify if there are disparities between our recruited research populations and local populations and develop a plan for studying and addressing disparities in HHT research.

Methods: We compared the Toronto HHT Centre’s recruitment to an international study [the Brain Vascular Malformation Consortium (BVMC)], to the general GTA and Ontario population (1). Specifically, we compared available data regarding age, sex, race, and ethnicity.

Results: Our Centre’s non-GTA recruits to the BVMC (n=326), included 27/326 (8.3%) visible minorities, compared to 29.3% of the general Ontario population. Our Centre’s GTA recruits to the BVMC (n=128), included 23/128 (17.9%) visible minorities, compared to 51.4% of the general GTA population. Our Centre’s non-GTA recruits to the BVMC (n=326), included 6/326 (1.8) Black people, compared to 4.7% of the general Ontario population. Our Centre’s GTA recruits to the BVMC (n=128), included 5/128 (3.9%) Black people, compared to 7.5% of the general GTA population. Our Centre’s non-GTA recruits to the BVMC (n=326), included 2/326 (0.6%) Indigenous people, compared to 2.8% of the general Ontario population. Our Centre’s GTA recruits to the BVMC (n=128), included 0/128 (0%) Indigenous people, compared to 0.8% of the general GTA population.

Conclusions: We report preliminary evidence of racial disparity between our Centre’s recruited research patients and the general population. It should be noted that this preliminary analysis is limited by the comparison to the general population, versus the clinic population or people with HHT. As such, it is unclear whether this disparity is occurring from barriers to clinical diagnosis, clinic referral, or research recruitment. Next steps will include engaging with communities, developing aims and an approach to EDI research in HHT.

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Abstract #54

Doxycycline Randomized Controlled Trial for Hereditary Hemorrhagic Telangiectasia - Study Design and Preliminary Results

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Introduction & Objectives: There is great interest in developing and studying novel therapies for epistaxis in hereditary hemorrhagic telangiectasia (HHT) given that it affects 90% of adult patients and impacts quality of life. Several recent randomized controlled trials (RCTs) of anti-angiogenic therapies for epistaxis have been negative, likely due to poorly characterized outcomes measures. This study investigates the effectiveness of oral doxycycline for the treatment of recurrent nasal hemorrhage in HHT subjects and aims to better characterize the measurement of epistaxis for clinical trials.

Methods: Patients are recruited to an ongoing phase II, double-blind, cross-over RCT of oral doxycycline for HHT-associated epistaxis. All patients receive a 6-month course of study drug and a 6-month course of placebo, with an intervening 6-month washout period. The study takes place over a period of 24 months, including a 3-month run in period and 3-month follow-up period. The primary outcome is the reduction of weekly epistaxis duration, as measured from daily patient diaries. Secondary outcomes include the regression of vascular malformations and biomarkers of relevant mechanistic pathways, including MMP9, VEGF, ANG2, IL6, and ENG, assessed through micro-imaging, tissue biopsy, and serum and plasma collection.

Results: We will present preliminary data regarding the measurement characteristics of the patient-reported outcome weekly epistaxis duration (PRO-WED) and its sensitivity to change by treatment period. Seven patients were included for analysis, with 98% completion of the daily diary. The average PRO-WED across all patients at baseline was 85.0 minutes, SD 92.3 and 65.6 minutes, SD 59.5 during treatment/placebo. Coefficient of variance for PRO-WED at baseline and during treatment/placebo was 0.49, SD 0.1, and 0.58, SD 0.2, respectively. Statistically significant changes in the mean PRO-WED from baseline to treatment/placebo were noted in six patients (86%). Only two patients (29%) had a significant change in epistaxis severity score (ESS), with both reporting decreased (improved) scores after treatment/placebo, as compared to baseline. Preliminary biomarker data will also be presented, as available.

Conclusion: In our preliminary results, PRO-WED was shown to be a feasible clinical trials measure, was reasonably stable during baseline measurement, and appeared to be variable with treatment state, suggesting it may provide a sensitive clinical trials outcome measure in HHT. Further analysis with all recruited subjects and after unblinding occurs will be important next steps.

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Abstract #55

Autotitrating Continuous Positive Airway Pressure Titration Compared to Laboratory-based Polysomnography Titration for the Treatment of Obstructive Sleep Apnea in Children with Complex Chronic Conditions

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Introduction: Children with complex chronic conditions (CCC) are disproportionately affected by obstructive sleep apnea (OSA), and a growing number require continuous positive airway pressure (CPAP). Early initiation of effective CPAP can improve treatment adherence, so timely titration is critical. Autotitrating CPAP (APAP) can be started at home prior to the laboratory-based polysomnography (PSG) titration study, but no studies have examined its use in children with CCC. Our study aimed to compare treatment pressures determined by APAP to those determined by PSG in children with CCC.

Methods. Retrospective study of children with OSA ≤18 years initiated on APAP. Patients without adequate PSG or APAP data were excluded. Median pressures (PMED) and average device pressures ≤95% of the time (P95) from APAP use downloads were compared to PSG-prescribed pressures (PPSG). Demographics, clinical characteristics, and PSG data were collected. Feudtner’s pediatric CCC classification system version 2 was used.

Results: Forty-eight patients met inclusion criteria. Mean age was 11.6 (SD 4.1) years, 65.3% were male, 64.6% had a CCC. APAP was used 4 hours/night for a median 59.0 (31.5, 81.8) % of nights. Median obstructive apnea-hypopnea index (OAHI) decreased from 15.0 (7.8, 26.7) events/hour on diagnostic PSG to 1.4 (0.5, 4.7) events/hour on titration PSG. Median PPSG was 8.0 (7.0, 9.3) cmH2O, PMED was 7.6 (6.8, 8.7) cmH2O, and P95 was 10.1 (8.9, 11.0) cmH2O. PMED and P95 both correlated with PPSG (r=0.37, p=0.01; r=0.28, p=0.05).

Conclusions. APAP-derived pressures correlated with and were close to final CPAP pressures determined by titration PSG. APAP was safe and generally well-tolerated. Initiation of APAP should therefore be considered in children with CCC who are awaiting their titration PSG. This mitigating strategy is imperative with long PSG waitlists in Canada, and especially now, with increased delays caused by the COVID-19 pandemic."
Abstract #56

Non-HLA Antibodies In Serum Prior To The Onset Of Chronic Lung Allograft Dysfunction


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Introduction: Non-human leukocyte antigen (HLA) antibodies have been associated with chronic lung allograft dysfunction (CLAD). Whether they predate CLAD is unclear. We hypothesized that patients destined to develop CLAD might develop non-HLA antibodies prior to CLAD onset.

Methods: In a single centre retrospective study, we examined 100 consecutive crossmatch negative recipients of a bilateral lung transplant between 1 January 2013 and 31 December 2014. Using a two-colour fluorescent antigen microarray with 152 unique antigens, we measured IgG and IgM autoantibodies in pre-transplant and six months post-transplant serum samples. L2o-gtransformed mean fluorescent intensities (MFIs) were determined for each antigen. CLAD was determined using published definitions. Significance analysis of microarrays (SAM) was used to analyze differences in antigen reactivity with a false discovery rate of 0.05. Paired and unpaired analyses were used to examine differences within and between recipients who developed CLAD within 5 years and recipients who remained CLAD free at 5 years post-transplant.

Results: Serum samples were available for 96 recipients - 35 (36.5%) developed CLAD and 61 remained CLAD-free within 5 years. Total IgM and IgG reactivity decreased in most patients post-transplant (Fig 1A), although IgM levels were stable in patients developing CLAD. Three IgM autoantibodies - including anti-club cell secretory protein (CCSP, Fig 1B) - increased in most patients post-transplant; this increase was of greater magnitude in patients later developing CLAD. Patients destined to develop CLAD also had an increase in IgG fluorescence directed at human core histones (Fig 1C).

Conclusion: Our results suggest that there may be important differences in non-HLA antibody reactivity that appear before the onset of CLAD. These observations, which require validation in further studies, may also indicate a specific role for non-HLA antibodies directed at club cell secretory protein and nuclear antigens in CLAD development.