Kate Verbeeten's Projects Completed During CPEG Fellowship, 2016-2017

In 2015 I was very fortunate to receive funding from CPEG to complete a third year research fellowship at the Children's Hospital of Eastern Ontario. My initial objective was to spend the year working with Dr. Margaret Lawson on the analysis of patient-reported outcomes from the CGM TIME Trial, a multicentre randomized controlled trial exploring the effect of timing of initiation of continuous glucose monitoring (CGM) on the outcomes of glycemic control and CGM adherence in children with type 1 diabetes switching from insulin injections to pump therapy. Partway through the year, there were unforseen events which resulted in the CGM TIME Trial work being delayed by several months. During this time I was able to work on unrelated projects, including the following:

- A review paper "The Role of Corticosteroid-Binding Globulin in the Evaluation of Adrenal Insufficiency" which was submitted for publication in July 2017
- A case report "Rectal Metyrapone for Treatment of Hypercortisolism in an Infant with McCune-Albright Syndrome, which was recently published in the *Journal of Pediatric Pharmacology and Therapeutics*
- A teaching booklet for students and residents working in the CHEO Diabetes Clinic
- A station for the National Canadian Pediatric Practice OSCE
- A case report "A Patient with Kabuki Syndrome and Multiple Mild Pituitary Abnormalities" which is nearly complete
- A genome-sequencing project (in collaboration with the CHEO Genetics team) involving a family with a disorder of carnitine metabolism

After completing my third year of fellowship I received an extension of funding from the Children's Hospital Academic Medical Organization to continue work on the CGM TIME Trial projects. The following manuscripts are in preparation:

- Analysis of the association between motivational stage of children and parents at the time of CGM initiation and the outcomes of change in HbA1c and CGM adherence 6 months after starting CGM.
- Description of changes in fear of hypoglycemia scores in children and parents as the children in the trial transitioned from insulin injections to insulin pump, ± CGM.

- Analysis of reported barriers to maintaining glycemic control and perceived self-care in children and parents participating in the CGM TIME trial, compared to their method of insulin delivery and CGM adherence.

I have included three abstracts from completed projects below:

Readiness for Making and Sustaining Behaviour Change at Initiation of Pump Therapy and Continuous Glucose Monitoring in Pediatric Diabetes
(K. Verbeeten, N. Sourial, J. Chan, M. Lawson; presented as a poster at the 2016 Canadian Diabetes Association Conference)

OBJECTIVES: To evaluate readiness for making and sustaining behaviour change at initiation of insulin pump +/- continuous glucose monitoring (CGM) using SOCRATES (Stages of Change Readiness and Treatment Eagerness Scale) and its relationship to glycemic control.
SUBJECTS: Parents, and children age ≥10 years with type 1 diabetes, participating in a multicentre trial comparing simultaneous pump and CGM to delayed CGM initiation (Paradigm™ Veo™ pump, Enlite™ sensor, Medtronic Canada).
METHODS: Participants completed SOCRATES at trial entry. Percentages of children and parents classified into each motivational stage were calculated with binomial proportion confidence intervals. Association between HbA1c and motivational stage was assessed with linear regression.
RESULTS: 96/99 eligible children and 137 parents completed SOCRATES. 90.6% of children and 93.4% of parents were classified into one motivational stage, with 50.0% of children and 46.0% of parents as Precontemplation. Parents were more likely to be classified as Action (39.4 vs. 17.7%) and children as Maintenance (21.9 vs. 5.8%). Few participants were classified as Contemplation or Determination (0-1.5%). HbA1c and motivational stage were significantly associated, with mean HbA1c lowest in Precontemplation and Contemplation. Mean age was similar between groups. Precontemplation had shorter duration of diabetes compared to Maintenance.
CONCLUSIONS: SOCRATES can categorize children with type 1 diabetes and parents into motivational stages. Many individuals about to start pump therapy +/- CGM were in the

Precontemplation Stage; their mean HbA1c may indicate reasons other than glycemic control for changing diabetes regimen. Ongoing research will determine if motivational stages can predict future diabetes behaviours, including CGM adherence.

The Role of Corticosteroid-Binding Globulin in the Evaluation of Adrenal Insufficiency
(K. Verbeeten and A. Ahmet; recently submitted for publication)

Cortisol is a hydrophobic molecule that is largely bound to corticosteroid-binding globulin (CBG) in the circulation. In the assessment of adrenal insufficiency, many clinicians measure a total serum cortisol level, which assumes that CBG is present in normal concentrations and with a normal binding affinity for cortisol. CBG concentration and affinity is affected by a number of common factors including oral contraceptive pills, fever, and infection, as well as rare mutations in the *SERPINA6* gene, and as such, total cortisol levels might not be the ideal way to assess adrenal function in all clinical circumstances. This paper reviews the limitations of immunoassay and liquid chromatography/tandem mass spectrometry (LC-MS/MS) in the measurement of total cortisol, the challenges of measuring free serum cortisol directly as well as the difficulties in calculating an estimated free cortisol level from total cortisol, CBG and albumin concentrations. Newer approaches to the evaluation of adrenal insufficiency, including the measurement of cortisol and cortisone in the saliva, are discussed and a possible future role for these tests is proposed.

Rectal Metyrapone for Treatment of Hypercortisolism in an Infant with McCune-Albright Syndrome

(K. Verbeeten, S. Hadjiyannakis, M. Cameron, J. McDonald; Journal of Pediatric Pharmacy and Therapeutics 2017; 22(3): 233-236)

Infantile Cushing syndrome is an infrequent yet potentially fatal manifestation of McCune-Albright syndrome, for which there are few safe treatments available. Ketoconazole is limited by potential hepatotoxicity in this population. Metyrapone may be an effective treatment, but it may

not be tolerated when given orally. An infant with McCune-Albright syndrome presented with severe Cushing syndrome. Oral metyrapone resulted in feeding refusal, and ketoconazole caused an increase in liver enzymes; however, she was successfully treated with metyrapone given rectally. The patient avoided a feeding tube, and her serum cortisol concentration was lowered to a safe level. Metyrapone given per rectum may be a safe and effective alternative to oral metyrapone in treating young children with Cushing syndrome.