Harold Amos Medical Faculty Development Program

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Institution: Duke University School of Medicine

Mentor(s): Dr. Edward Wong

College: Wesleyan College

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Residency: Duke University Medical Center

Fellowship: McGaw Medical Center of Northwestern University

Title of Project: Apheresis Specific Outcomes to Facilitate a Clinical Trial in Heparin-Induced Thrombocytopenia

**Background**: Autoimmune disorders like heparin-induced thrombocytopenia (HIT) cause death and disability in over 24 million Americans; but > 50% of these disorders can be treated with therapeutic plasma exchange (TPE). Despite TPE’s effectiveness, however, TPE is associated with increased morbidity, including higher hospital length of stay (LOS), increased number of ICU days, and, in some patient populations, increased mortality. Improving TPE-specific outcomes has proven difficult, largely due to the fact that single institutional studies for any one apheresis-treated disorder are limited by small sample sizes and disease-specific outcomes. However, apheresis-specific outcomes are needed to determine TPE’s impact and thus improve outcomes. Our hypothesis is that apheresis-specific outcome measures can be developed and applied to a multicenter study of HIT. To test this hypothesis, we will use multivariable modeling to determine the impact of TPE on hemostasis and thrombosis outcomes in patients with HIT.

**Interim Methods**: In a cross-sectional analysis of the National Inpatient Sample (2010-2014) and a retrospective single institution study (2012-2017), we identified patients with a diagnosis of HIT treated with or without TPE. Patient characteristics included age, sex, race, diagnoses, procedures, and comorbidities. Comorbidity burden per hospitalization was quantified using the Elixhauser comorbidity index, a validated numeric score that describes the comorbidity index. The primary outcome was in-hospital mortality, defined as death at any time during the hospitalization. Secondary outcomes included major bleeding, thrombotic complications, LOS, and hospital charges. The thrombotic complications variable was comprised of venous thromboembolism, pulmonary embolism, arterial thrombosis, amputation, and thrombotic stroke (cerebral artery thrombosis). Major bleeding was comprised of intracranial, gastrointestinal, genitourinary, hemarthrosis, pulmonary, and other bleeding

**Interim Results**: Our single institution study identified 24 patients who received TPE for HIT. Thromboembolic complications occurred in three patients (12.5%) within 7 days of TPE. Thirty-day mortality rate was 12.5% and were adjudicated to be unrelated to the TPE procedure. Our cross-sectional analysis identified 22,165 cases with HIT, among which 90 (0.4%) received TPE, corresponding to national weighted estimates of 106,435 HIT and 439 TPE-treated HIT cases. TPE was not associated with decreased in-hospital mortality (OR = 1.72; 95%CI: 0.93-3.17, p = 0.085 but was associated with a higher likelihood of major bleeding (OR = 2.35; 95%CI: 1.40-3.68, P = 0.0009) TPE was also associated with higher hospital LOS (20.5 vs 10 days, p < 0.0001) and charges (USD 211181 vs USD 81654, P < 0.0001).

**Interim Conclusions**: TPE treatment in HIT is associated with increased bleeding complications. A multi-center retrospective and prospective study is currently underway to further study bleeding outcomes of TPE-treated patients with HIT.

Harold Amos Medical Faculty Development Program

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Title of Project: HRQOL, decision making, and molecular determinants of spine metastasis

Metastatic spine disease affects a significant proportion of cancer patients, and can lead to severe adverse effects, including sensory disturbances, weakness, pain, bowel/bladder incontinence and/or paralysis. The prevalence of metastatic spine disease and the functional sequelae of the disease are expected to increase due to advancements in screening, detection, and therapies. Patients with metastatic spine disease have poor prognoses and are at risk for low health-related quality of life (HRQOL). Few studies have examined patient-specific factors or interventions that influence and/or improve quality of life in this population. Furthermore, prognostication and management rely almost exclusively on clinical and imaging parameters, and thus, patient-specific priorities, preferences, and expectations are rarely elicited within the clinical decision-making landscape. Moreover, although studies have demonstrated that significant disparities exist in health outcomes and satisfaction between different sociodemographic groups (i.e. race, gender, income status, and education) in a variety of non-spine disease types, the impact of these factors on HRQOL and clinical outcomes for patients diagnosed with metastatic spine disease remains unclear. Furthermore, genomic predictors of tumor progression in spine metastasis are lacking, with tumor type providing the best indication of prognosis. During the course of fellowship period, I have completed several studies examining the full continuum of administered care for patients diagnosed with spine metastasis. Using quantitative and qualitative analyses, we examined patient and provider priorities, perceptions of interventions for metastatic spine disease, patient–provider communication, and the influence of sociodemographic factors on communication and clinical outcomes. Through analysis of the National Inpatient Sample database, we found on multivariable analysis that black patients and males were more likely to present with more severe disease, black surgical patients had increased risk of perioperative morbidity, and females and blacks were less likely to receive surgical intervention. To obtain a more granular analysis, I served as the project lead examining the influence of gender on health-related quality of life and outcomes for patients undergoing surgical intervention and/or radiotherapy and found that although female patients had better survival and better outcomes, they did not achieve the same benefit in HRQOL as males. Furthermore, we assessed the influence of interventional factors on clinical outcomes ranging from interventions to improve neurologic function, preoperative optimization, nutrition consults, radiotherapy advances, prognostic calculators, spinal alignment, and hospital-based characteristics for patients diagnosed with spine metastasis. Finally, using single cell RNA sequencing analysis of human spine metastasis clinical specimens obtained from the neurosurgical operating room, we were able to identify differences in gene expression, and cell subsets and normal versus tumor bearing vertebral bodies in the same patient. Studies will increase our understating of the determinants of spine metastasis and lead to the development of preclinical models and therapies to improve outcomes.

Harold Amos Medical Faculty Development Program

Name: Joshua J. Joseph, MD, MPH, FAHA

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Medical/Dental/Nursing PhD School: Boston University School of Medicine

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Fellowship: Johns Hopkins University School of Medicine

Title of Project: Association of Serum Aldosterone and Plasma Renin Activity With Ambulatory Blood Pressure in African American – The Jackson Heart Study

BACKGROUND: The renin-angiotensin-aldosterone system (RAAS) is an important driver of blood pressure (BP), but the association of the RAAS with ambulatory BP (ABP) and ABP monitoring phenotypes among African Americans has not been assessed.

METHODS: ABP and ABP monitoring phenotypes were assessed in 912 Jackson Heart Study participants with aldosterone and plasma renin activity (PRA). Multivariable linear and logistic regression analyses were used to analyze the association of aldosterone and PRA with clinic, awake, and asleep systolic BP and diastolic BP (DBP) and ABP monitoring phenotypes, adjusting for important confounders.

RESULTS: The mean age of participants was 59Å}11 years and 69% were female. In fully adjusted models, lower log-PRA was associated with higher clinic, awake, and asleep systolic BP and DBP (all P<0.05). A higher log-aldosterone was associated with higher clinic, awake, and asleep DBP (all P<0.05). A 1-unit higher log-PRA was associated with lower odds of daytime hypertension (odds ratio [OR] 0.59 [95% CI, 0.49–0.71]), nocturnal hypertension (OR, 0.68 [95% CI,0.58–0.79]), daytime and nocturnal hypertension (OR, 0.59 [95% CI, 0.48–0.71]), sustained hypertension (OR, 0.52 [95% CI, 0.39–0.70]), and masked hypertension (OR 0.75 [95% CI, 0.62–0.90]). A 1-unit higher log-aldosterone was associated with higher odds of nocturnal hypertension (OR, 1.38 [95% CI, 1.05–1.81]). Neither PRA nor aldosterone was associated with percent dipping, non-dipping BP pattern, or white-coat hypertension. Patterns for aldosterone:renin ratio were similar to patterns for PRA.

CONCLUSIONS: Suppressed renin activity and higher aldosterone:renin ratios were associated with higher systolic BP and DBP in the office and during the awake and asleep periods as evidenced by ABP monitoring. Higher aldosterone levels were associated with higher DBP, but not systolic BP, in the clinic and during the awake and asleep periods. Further clinical investigation of novel and approved medications that target low renin physiology such as epithelial sodium channel inhibitors and mineralocorticoid receptor antagonists may be paramount in improving hypertension control in African Americans.

Harold Amos Medical Faculty Development Program

Name: Rasheeda K. Hall MD, MBA, MHS

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Residency: Internal Medicine, Duke Department of Medicine

Fellowship: Nephrology, Duke Department of Medicine

Title of Project: Establishing Evidence to Manage Geriatric Syndromes in Dialysis Patients

Problem: Compared to older adults without kidney disease, older dialysis patients are twice as likely to fall, develop severe cognitive impairment, and become hospitalized. These adverse outcomes are associated with potentially inappropriate medications (PIMs). PIMs are medications such as benzodiazepines and anticholinergics that should be avoided in older adults because their risks usually outweigh their benefits. Older dialysis patients are more susceptible to adverse effects of PIMs because of altered medication clearance, blood pressure fluctuations during dialysis, and comorbid cerebrovascular disease. Given this susceptibility, reduction of PIMs is a logical first step towards improving quality of care for these vulnerable patients.

Objective: The objective is to develop an evidence-based strategy to reduce PIM use in older dialysis patients. Dr. Hall’s concurrent NIH grant examines prescribing patterns of specific PIMs, risk of hospitalization associated with those PIMs, stakeholder input from patients aged ≥65 years, and a subsequent pilot deprescribing intervention. To complement that grant, the AMFDP award supports specific studies in young, frail adults to uncover the following evidence: 1) prescribing patterns of specific PIMs and their associated risk in frailty incidence (among non-frail) and/or functional decline, and 2) insight into elements of a deprescribing intervention from younger, frail dialysis patients.

Approach: We use the United States Renal Data System to conduct epidemiologic studies on PIM prescribing patterns and risk of harm. PIMs of interest include alpha blockers, central alpha agonist, opioids, muscle relaxants, sedatives, and anticholinergics. To inform pilot design, we conducted qualitative study with 53 clinicians (dialysis, primary care, and pharmacists) and 21 patients/caregivers (11 were aged 55-64 years).

Findings: Using a cohort of older adults new to dialysis (2013-2014), we found that continuation of an antihypertensive PIM after dialysis initiation was not associated with increased hospitalization or mortality risk. *BMC Nephrol* 22, 232 (2021). Key themes to inform pilot design were: 1) clinicians have limited communication, time, and knowledge, and 2) patients trust primary clinician opinion, prefer fewer medications, but also value symptom relief.

Next steps: 1) Pilot deprescribing model of care at local dialysis clinics; 2) Conduct pharmacoepidemiologic study to identify extent of association of PIMs with onset of frailty and functional decline in adults receiving dialysis.