ARIC Manuscript Proposal # 3139

PC Reviewed: 3/20/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Hospitalization with Infection and Subsequent Risk of Incident End-Stage Renal Disease: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters):
Infection and incident ESRD

2. Writing Group:
Writing group members:
Junichi Ishigami, Logan Cowan, Ryan Demmer, Morgan Grams, Pamela Lutsey, Josef Coresh, Kunihiro Matsushita, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __J. I._ **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Data ascertainment for the present study has been already completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Despite improvement of diagnosis and treatment, infectious disease is a still leading cause of death worldwide.[1] In addition to direct consequences of infectious disease, a body of evidence demonstrates the increased risk of cardiovascular disease[234,5] after an episode of acute infection. Excessive immune responses (e.g., tumor necrosis factor-α and interleukin-1[6,7]) contribute to increased cardiovascular risk.

Those immune responses would be relevant for kidney function as well.[8] Indeed, infectious disease such as sepsis is recognized as a risk factor for acute kidney injury.[9,10] However, little is known about the long-term kidney outcomes following an episode of acute infection. To our knowledge, only one study from Taiwan reported a modestly increased (~14%) risk of incident end-stage renal disease (ESRD) over up to 13 years after hospitalization for pneumonia.[11] However, this study restricted to a specific type of pneumonia due to pneumococcus as a potential risk factor for kidney disease progression.

To comprehensively tackle this study question, we aim to assess the association of incident hospitalization with several types of infection with subsequent risk of ESRD in a community cohort, the Atherosclerosis Risk in Communities Study. We are specifically interested in the following four most common types of infection responsible for hospitalizations in the US: pneumonia, urinary tract infections, cellulitis, and osteomyelitis, and bloodstream infections.[12] As a secondary outcome, we will also explore incident chronic kidney disease (CKD).[13]

5. Main Hypothesis/Study Questions:

Hospitalization with infection is associated with increased risk for ESRD and incident chronic kidney disease (CKD).

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design:

As detailed in "Statistical Analysis Plan" below, we will apply a few approaches to comprehensively explore the study question.

Inclusion/exclusion criteria:

Participants who are neither white nor African American, had ESRD at the time of incident hospitalization with infection, or had missing covariates will be excluded from analysis.

Exposure

Exposure of interest will be incident hospitalization with four types of infection (pneumonia, urinary tract infections, cellulitis and osteomyelitis, and bloodstream infections) from ARIC visit 1 (1987-1989) through December 31, 2013. Events will be identified from hospital discharge records using relevant *International*

Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) codes (i.e., pneumonia [480-486]; urinary tract infections [590.1, 599.0, and 601.0], cellulitis and osteomyelitis [040.0, 681, 682, and 730.0-2], and bloodstream infections [038, 054.5, 785.52, 790.7, 995.91, and 995.92]). For those who had multiple hospitalizations with infection, our primary analysis will be based on first episode, but secondarily we will take into account multiple infections, as described in Statistical Analysis Plan.

For primary analysis, we will include all cases of infection regardless of diagnostic position. Since patients who have infection in secondary diagnostic position would have other primary cause of hospitalization complicating the clinical course, we will also conduct a secondary analysis by restricting to cases with infection diagnosis at the primary position.

Outcome

The primary outcome of interest is incident ESRD, defined as initiation of dialysis, receiving kidney transplantation, or death due to CKD. Events of incident ESRD will be ascertained through the linkage to the United States Renal Data System. The secondary outcome is incident CKD, defined as any one of the following criteria 1) incident ESRD defined above, 2) a first record of eGFR <60 ml/min/1.73m^2 at follow-up visit accompanied by 25% or greater decline compared to the closest previous visit, 3) hospitalization or death with a diagnosis of CKD.[13]

Other variables of interest and covariates:

Covariates at baseline visit include age, gender, race, body mass index (BMI), smoking status (current/former vs. never smoker), alcohol consumption, years of education, eGFR (based on CKD-EPI equation using serum creatinine), and medical history (diabetes, hypertension (HTN), chronic obstructive pulmonary disease (COPD), cancer, heart failure (HF), coronary heart disease (CHD), and stroke). Covariates will be updated over time whenever possible until an infection occurs, and for covariates that are only assessed at follow-up visits such as BMI and eGFR, values available at the closest visit will be used.

Statistical Analysis Plan:

We will use two approaches to assess the association between hospitalization with infection and risk of incident ESRD: 1) time varying covariate analysis,[14,15] and 2) nested case control study using incidence density sampling methods.[2,16]

1) Time-varying exposure analysis

Using data at visit 1 as baseline, incident hospitalization with infection will be entered in multivariable Cox regression models as a time-varying exposure.

2) Nested case-control study

The nested case-control design using incidence density sampling methods is an alternative efficient approach to assess the contribution of infection to the subsequent adverse outcomes.[16] We will first identify cases of hospitalization

with infection, and then match them to 1 to 2 controls. For control selection, we will match on several key demographic (e.g., age, sex, and race), and clinical factors (e.g., diabetes, cardiovascular disease, eGFR, # of hospitalization). Then, the risk of each outcome (e.g., ESRD and incident CKD) will be compared between cases and controls using multivariable Cox proportional hazards models.

Multivariable models

Using double robustness estimation, the models will be adjusted for age, sex, race, BMI, smoking status, alcohol consumption, education level, history of HTN, diabetes, COPD, cancer, HF, CHD, and stroke, and eGFR.

Sensitivity analyses

We will consider competing risk models accounting for all-cause mortality as competing events. Since patients who developed AKI during hospitalization with infection may have a higher risk of adverse kidney outcomes, we will also perform sensitivity analysis excluding patients discharged with a diagnosis of AKI (ICD-9CM, 584.9).

Furthermore, incidence of hospitalization with cardiovascular disease may mediate the association between infection and incident ESRD. We will adjust for incident cardiovascular disease (e.g., coronary heart disease, heart failure, and stroke) as a time varying covariate.

Finally, we will separately analyze the association of each type of infection and subsequent risk of incident ESRD and CKD (i.e., all four types would be included as time-varying exposures in time varying exposure analysis; or each will be analyzed in turn while the other three would be simply included in control in nested case control study). We will also perform subgroup analysis by age (65+ vs. <65 years), sex (men vs. women), race (white vs. black), and status of diabetes (yes vs. no).

Limitations

Cases of hospitalization with infection will be ascertained using infection ICD-9CM codes, which could lead to misclassification. Also, mild cases of infection not requiring hospitalization will not be captured.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __ X __ Yes _ _ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?

____ Yes _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?

____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MP2391 "Hospitalized infection as a trigger for acute ischemic stroke in the ARIC study" studied the relationship between hospitalization with infection and subsequent risk of ischemic stroke. Our outcome of interest will be incident ESRD and CKD. The first author of MP2391 is included in the present MP.

MP 2624 proposed in 2015 "Chronic Kidney Disease and Risk for Infection-Related Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study" assessed the association of CKD with risk for infection. The primary exposures of interest in the present study will be mineral and bone biomarkers though we will adjust for eGFR. Most of the authors of MP2624 including the first author are included in the current proposal.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* _ 2002.02, 2009.17 **__)**

__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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