ARIC Manuscript Proposal #2624

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Chronic kidney disease and risk for infection in the community: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters):
CKD and infection

2. Writing Group:
Writing group members:
Junichi Ishigami, Morgan Grams, 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:

Chronic kidney disease (CKD), reduced estimated glomerular filtration rate (eGFR) and/or presence of albuminuria,[1] is a rapidly growing public health problem. CKD affects 13% of adults in the United States[2] and is associated with adverse health outcomes.[3] Although cardiovascular disease is often considered as the most important complication of CKD, infection is another clinical burden particularly among those on dialysis.[4,5] Indeed, infection is a second leading cause of death and comprises one fifth of hospitalizations among dialysis population.[6] Bloodstream infection in hemodialysis[7] and peritonitis in peritoneal dialysis[8] are two major infectious diseases in this population, but other infections such as pneumonia and cellulitis are also relevant,[9,10] suggesting the contribution of uremic toxin to impairment of immune response.[11]

Regarding earlier stages of CKD not requiring dialysis, a few studies reported that mildly to moderately reduced kidney function is significantly associated with some types of infection such as bloodstream infection,[12] pneumonia,[13,14] and genitourinary infection.[14] However, these studies investigate clinical population or older adults, raising some uncertainties on the association of reduced kidney function with the risk of infection in the general population.

Moreover, it is of importance that data for the other key element of CKD, albuminuria, in the context of infection risk are sparse despite its plausible link to infection. Specifically, glycocalyx is one of the main components of endothelial surface layer and its degeneration is associated with development of albuminuria.[15] A recent study demonstrated that glycocalyx regulates neutrophil adhesion in animal models of sepsis.[16] Albuminuria is commonly seen in critically ill sepsis patients,[17] and is positively associated with the disease severity.[18] To our knowledge, only one study with diabetic patients reported that elevated albuminuria remained as one of the significant predictors of infection-related hospitalization,[19] but no study has simultaneously assessed eGFR and albuminuria for their contributions to the risk of infection in the community.

Thus, the aim of the study is to comprehensively explore the association of both CKD measures, eGFR and albuminuria, with the risk of infection in a bi-ethnic community-based cohort, the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

Decreased eGFR and elevated albuminuria are independently associated with risk for infection.

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).

Inclusion criteria

- All ARIC study participants whose serum creatinine and urine albumin/creatinine ratio (ACR) are measured.
- White and black participants.

Exclusion criteria

- Participants whose serum creatinine or ACR are not available.
- Non-black/non-white participants.

Exposures

- CKD measures (given the availability of albuminuria and subsequent outcomes, visit 4 will be used for primary analysis but prior visits will be used for sensitivity analysis)
  - eGFR: calculated from CKD-EPI equations based on serum creatinine and/or cystatin C
    - eGFR will be modeled as continuous variable with its splines and also will be stratified to the following categories: ≥105, 90-104, 75-89, 60-74, 45-59, 30-44, 15-29, and <15 ml/min/1.73m^2 [3]
  - Kidney damage marker
    - Urine ACR (will be treated as continuous and categorical [<10, 10-29, 30-299, and ≥300 mg/g] variables)[3]

Outcome

- Hospitalizations for infection[20] (ICD codes: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383, 386.33, 386.35, 388.60, 390–393,421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0,475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494,510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3,540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3,575–575.12, 590–590.9, 595–595.4, 597–597.89, 598.0,599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4,611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9,706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8,996.60–996.69, 997.62, 998.5, and 999.3 [details in Supplemental table 1 on pages 7-8])
- While we will primarily use hospitalization ICD codes for outcome ascertainment, we will also explore data from CMS for sensitivity analysis.

Other variables of interest and covariates:

- Age
- Gender
- Race
- Body mass index (BMI)
- Smoking status (never or ever smokers)
- Alcohol consumption
- Level of education as social economic status (SES)
- Hypertension
- Sitting blood pressure (systolic and diastolic)
- Diabetes
- History of cardiovascular disease (at baseline and as time-varying covariate)
- Inflammatory biomarker (hsCRP)
- Incident end-stage renal disease (from USRDS linkage)

Statistical Analysis Plan:

- Baseline characteristics will be compared between with and without any event of infection-related hospitalization as well as across eGFR and ACR categories.
- Incidence rate of infection hospitalizations will be calculated according to CKD measures and status.
- Cox proportional hazard models will be used to quantify the association of CKD measures with the risk of hospitalization with infection.

- Models will be adjusted for variables listed above.
- Overall infection hospitalizations will be our primary outcome, but organ-specific infection (e.g., pneumonia, sepsis) will be analyzed secondarily.
- Several sensitivity analyses will be performed. First, we will repeat the analysis in key demographic and clinical subgroups to assess potential effect modifiers. Second, we will analyze the data only using the ICD-9 codes as a primary diagnosis. Third, we will adjust the model for incident end-stage renal disease as a time varying variable to take account for initiating dialysis. Finally, we will explore whether incidence of infection-related hospitalization changes over the period of before and after initiating dialysis.

Limitations

- Outcome ascertainments rely on ICD codes, and therefore relatively mild cases of infection without requiring hospitalization, may not be captured. However, we will try to check consistency with CMS data. Another concern is that due to the nature of observational study, residual confounders might be remained even after adjustment for various confounders.

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)?

To our knowledge, there is no other ARIC proposal focusing on the association between CKD and infection.

MP 1348 proposed in 2008 "Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study" includes all hospitalizations, but our proposal would focus on overall and organ-specific infectious diseases. Also, our proposal will explore CMS data as well. A key author of MP 1348, Josef Coresh, is 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 **)**

__ 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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Supplemental table 1: Cause of the infection and ICD-9-CM codes

ICD-9	Referred disease description
001–139	Infectious and parasitic diseases
254.1	Abscess of thymus
320–326	Diseases of the nervous system
331.81	Rye's syndrome
372–372.39	Conjunctivitis
373.0–373.2	Inflammation of eyelids (Blepharitis, Chalazion)
382–382.4	Suppurative and unspecified otitis media
383	Mastoiditis
386.33	Suppurative labyrinthitis
386.35	Viral labyrinthitis
388.6	Otorrhea
390–393	Rheumatic Fever
421–421.1	Acute and subacute endocarditis
422	Acute myocarditis
422.91–422.93	Acute myocarditis, idiopathic
460–466	Acute respiratory infections
472–474.0	Chronic pharyngitis and nasopharyingitis
475–476.1	Peritonsillar abscess
478.21–478.24	Other diseases of upper respiratory tract
478.29	Other diseases of upper respiratory tract
480–490	Pneumonia and influenza (480–488), Bronchitis, not specified as acute or chronic (490)
491.1	Mucopurulent chronic bronchitis
494	Bronchiectasis
510–511	Empyema (510) and pleurisy (511)
513	Abscess of lung and mediastinum
518.6	Allergic bronchopulmonary aspergillosis
519.01	Infection of tracheostomy stoma
522.5	Periapical abscess without sinus
522.7	Periapical abscess with sinus
527.3	Abscess of salivary gland
528.3	Cellulitis and abscess of oral soft tissues
540–542	Appendicitis
566–567.9	Abscess of anal and rectal regions
569.5	Abscess of intestine
572–572.1	Liver abscess and sequelae of chronic liver disease
573.1–573.3	Hepatitis, toxic
575–575.12	Other disorders of gallbladder

590–590.9	Infections of kidney
595–595.4	Cystitis
597–597.89	Urethritis, not sexually transmitted, and urethral syndrome
598	Stricture, urethral, unspecified infection
599	Urinary tract infection, unspecified/pyuria
601–601.9	Inflammatory diseases of prostate
604–604.9	Orchitis and epididymitis
607.1	Balanitis
607.2	Other inflammatory disorders of penis
608	Seminal vesiculitis
608.4	Other inflammatory disorders of male genital organs
611	Inflammatory disease of breast
614–616.1	Inflammatory disease of ovary fallopian tube pelvic cellular tissue and peritoneum
616.3–616.4	Abscess of Bartholin's gland, Other abscess of vulva
616.8	Other specified inflammatory diseases of cervix vagina and vulva
670	Major puerperal infection
680–686.9	Infections of skin and subcutaneous tissue
706	Acne varioliformis
711–711.9	Arthropathy associated with infections
730–730.3	Osteomyelitis, periostitis, and other infections involving bone
730.8–730.9	Osteomyelitis, periostitis, and other infections involving bone
790.7–790.8	Bacteremia (not septicemia), Viremia, unspecified
996.60–996.69	Infection and inflammatory reaction due to internal prosthetic device implant and graft
997.62	Infection of amputation stump, unspecified extremity
998.5	Postoperative infection not elsewhere classified
999.3.	Other infection due to medical care not elsewhere classified