ARIC Manuscript Proposal #1960

PC Reviewed: 7/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between pneumonia hospitalization and acute cardiovascular events

b. Abbreviated Title (Length 26 characters): Pneumonia and cardiovascular disease

2. Writing Group:

Writing group members: Sachin Yende, Aaron Folsom, Laura Loehr, and Vicente Corrales-Medina, and other CHS co-authors.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Aaron Folsom
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3. Timeline: December 2012.

4. Rationale:

Hospitalization for infection and sepsis has long lasting effects. For example, in Health Aging, and Body Composition (Health ABC) cohort, we showed that older adults hospitalized for pneumonia had high 1 and 5-yr mortality, similar to mortality for hospitalization for a fracture.[1] Similarly, in the ARIC study, 1-yr mortality after pneumonia hospitalization was 25.7%. Infection and sepsis incidence rates continue to rise.[2] Improvements in hospital and intensive care unit care have reduced short-term mortality.[3] Thus, the number of adults at-risk for long-term sequelae after sepsis is increasing.

Of the various long-term consequences of sepsis, cardiovascular disease (CVD) is important because it is common and leading cause of death. For instance, in a cohort of individuals hospitalized for pneumonia (Genetic and Inflammatory Markers of Sepsis, GenIMS, n=2,320), we showed that CVD accounts for a third of deaths over 1 yr.[4] In the Health ABC study, we showed that CVD is a leading cause of re-hospitalization after community-acquired pneumonia (CAP), occurring in 19% over 5 years.[1] We have also conducted preliminary animal studies and showed that sepsis accelerates atherosclerosis. If pneumonia is associated with higher risk of long-term CVD, then preventive strategies could be targeted to patients recovering from pneumonia to improve long-term outcomes.

Using case series and case-control designs, several studies have shown that respiratory infections are associated with increased risk of CVD.[5-9] Recent studies also suggest that there may be higher risk of venous thromboembolism. There are 2 important limitations of these studies. First, these studies assessed only short-term risk of CVD (up to a few months). Second, individuals who are hospitalized with infection may have higher burden of risk factors for CVD (e.g. diabetes and smoking) and subclinical CVD. None of these studies adequately controlled for these risk factors.

5. Main Hypothesis/Study Questions:

We hypothesize that pneumonia hospitalization will be associated with higher risk of subsequent acute cardiovascular events.

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).

We will combine subjects enrolled in CHS and ARIC because participants in both cohorts had individuals with non-overlapping age ranges and both cohorts were enrolled during the same time period. Additionally, we have recently identified pneumonia events and developed a risk prediction score to predict pneumonia in both CHS and ARIC (ancillary study number 2010.22).

We will use 2 approaches: time-varying covariate analysis and propensity-matched analysis.

Time-varying covariate analysis

Pneumonia will be considered as a time-varying covariate in the Cox survival model and outcome measure will be time to first cardiovascular event. Analysis will be adjusted for baseline characteristics, including demographics (age, sex, and race), propensity for pneumonia (propensity score based on age, smoking, and lung function), and risk for cardiovascular disease (Framingham risk score and subclinical CVD).

Propensity-matched analysis

We will match participants hospitalized with pneumonia to those who have the same risk of pneumonia and cardiovascular events. We will use incidence density sampling where subjects will be categorized each year into those hospitalized with and without pneumonia. We will match each participant with pneumonia to 2 participants without pneumonia based on the following criteria: i.) similar propensity of developing pneumonia, ii.) similar propensity of cardiovascular disease (Framingham risk score using baseline variables and sub-clinical CVD), v.) frequency of cardiovascular events occurring at baseline or between enrollment and occurrence of pneumonia. We will then determine risk of subsequent acute cardiovascular events. We will compare incidence rates of cardiovascular events in participants hospitalized with pneumonia and matched participants. Event rates will be defined as the number of cardiovascular events divided by person-years. Person-years will be measured from date of pneumonia hospitalization to date of death or censoring, whichever came first. Data will be censored at10 years. We propose to limit the study follow-up to 10 years because baseline risk factors may be less predictive of risk of

pneumonia and CVD after 10 years. Poisson or negative binomial models will be used to compare incidence rates between the 2 groups.
Both approaches have strengths and limitations. For example, time-varying covariate analysis cannot determine association between pneumonia and acute cardiovascular events if a cardiovascular event occurs before pneumonia hospitalization. Matching may be inadequate for the propensity-matched analysis. However, this analysis can account for multiple cardiovascular events after pneumonia. Furthermore, participants with pneumonia have lower survival and comparing incidence rates accounts for different exposure time between the groups.

Outcome variable will be acute cardiovascular event, including stroke, myocardial infarction, and definite fatal cardiovascular heart disease. Sensitivity analysis will be performed after additionally incorporating revascularization procedures (bypass surgery, percutaneous coronary interventions, and carotid revascularizations). Other endpoints including venous thromboembolism will also be assessed.

Pneumonia – we have identified pneumonia hospitalization in both cohorts using ICD-9 codes 481-486. Additionally chart review to assess accuracy of the diagnoses was conducted in a subset.

Sensitivity analyses will include revascularization procedures as outcome measure and using more specific definitions for hospitalizations for pneumonia (ICD-9 codes 481, 482, 489 and were included in the primary discharge diagnosis field).

Sample size calculation: Together CHS and ARIC includes 21,680 participants. Of these 1,361 were hospitalized with pneumonia within the first 10 years at least once. We therefore anticipate having adequate power for the primary analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __x__ 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? ____ Yes ____ No
(This file ICTDER03 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. Not applicable.

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)?
None.

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

___ A. primarily the result of an ancillary study (list number* _____)
_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _2010.22_____ _____ _____)

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

12. 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.