Letters

COMMENT & RESPONSE

Hospitalization for Pneumonia and Risk of Cardiovascular Disease

To the Editor The study by Dr Corrales-Medina and colleagues[1] showed that hospitalization for pneumonia was associated with enhanced short-term and long-term risks of cardiovascular disease (CVD), including myocardial infarction, stroke, and fatal coronary artery disease. There are several methodological and clinical issues that need to be addressed to further examine the association between pneumonia and CVD.

Although the authors correctly excluded statin use from the analysis, the concomitant use of aspirin was not considered as a potentially confounding factor. Because cases and controls in both cohorts had atherosclerotic risk factors such as hypertension, diabetes, and dyslipidemia, these patients may have been taking aspirin. An observational study[2] performed in 1005 patients with pneumonia demonstrated that at 30 days, long-term aspirin use was associated with lower mortality and nonfatal CVD.

The authors included 2 cohorts with differences in age. The mean age in the Cardiovascular Health Study (CHS) was 73 years and the mean age in the Atherosclerosis Risk in Communities (ARIC) study was 55 years. The risk of CVD was associated with age because at 30 days from admission, CVD occurred in 10.6% of the older population compared with 0.9% of the younger population. This finding is consistent with our study showing an 11% incidence of myocardial infarction during the hospital stay in a cohort with a mean age of 70 years affected by pneumonia.[3]

In addition to age, another factor that increases the risk of CVD is the severity of pneumonia. Previous reports from the same authors and our group[3,4] showed that pneumonia severity score was independently associated with CVD. There is a discrepancy between these previous findings and the present study that showed no association between pneumonia severity and CVD risk.

Based on these considerations, we believe that older patients with severe pneumonia should be primarily considered for CVD prevention and that randomized clinical trials to assess approaches to reduce the risk of CVD in patients with pneumonia are warranted.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA*. 2015;313(3):264-274.

2. Falcone M, Russo A, Cangemi R, et al. Lower mortality rate in elderly patients with community-onset pneumonia on treatment with aspirin. *J Am Heart Assoc*. 2015;4(1):e001595.

3. Cangemi R, Casciaro M, Rossi E, et al. Platelet activation is associated with myocardial infarction in patients with pneumonia. *J Am Coll Cardiol*. 2014;64(18):1917-1925.

4. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation*. 2012;125(6):773-781.

In Reply Dr Violi and colleagues raise the possibility that an association between hospitalization for pneumonia and subsequent increase in CVD risk may be confounded by differential use of aspirin prior to the occurrence of pneumonia. We did not include aspirin usage because it was missing in 11% to 40% of participants at various time points during the first 10 years of follow-up in the CHS. The **Table** shows

Table. Frequency of Aspirin Use Prior to Pneumonia in the Cardiovascular Health Study

	Previous Aspirin Use, No./Total (%)[a]		
	Pneumonia Cases	Controls	P Value
Primary analysis[b]			
Participants but not controls hospitalized for pneumonia	405/591 (68.5)	818/1182 (69.2)	.77
Sensitivity analyses[b]			
Participants hospitalized for pneumonia and controls hospitalized for other reasons	422/614 (68.7)	422/614 (68.7)	>.99
Participants but not controls hospitalized for pneumonia (primary discharge diagnosis for participants)	264/379 (69.7)	518/758 (68.3)	.65
Participants but not controls hospitalized for pneumonia (no concomitant diagnosis of heart failure during hospitalization)	351/516 (68.0)	708/1032 (68.6)	.81

[a] Aspirin use was collected annually for the first 10 years and calculated using either data collected at baseline or at the last available time point prior to pneumonia hospitalization.

[b] Primary and sensitivity analyses as outlined in the main study.

aspirin use based on data collected at baseline and at additional time points prior to hospitalization for pneumonia if these data were available. Aspirin use was similar between the 2 groups, suggesting that confounding by unaccounted aspirin use is unlikely.

We agree with the authors that advanced age is an important risk factor for CVD after pneumonia. This is supported by the substantial difference in incident CVD after hospitalization for pneumonia between the 2 cohorts that we analyzed (CHS: mean age of 73 years and 10-year risk of 35% for CVD vs ARIC study: mean age of 55 years and 10-year risk of 16.5% for CVD). In regard to their point about the severity of pneumonia being an important risk factor for subsequent CVD, we also agree that previous studies support this concept. However, our study was not designed to address this question. Instead, we chose to perform a stratified analysis by pneumonia severity to determine whether the association between hospitalization for this infection and increased risk of CVD was present in cases of both severe and nonsevere pneumonia.

We agree with Violi and colleagues that randomized clinical trials of interventions to reduce CVD after hospitalization for pneumonia are needed, and that older adults with severe pneumonia would be a high-risk group in which these interventions could demonstrate benefit.

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Sedation Protocol for Critically Ill Pediatric Patients

To the Editor In the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial, Dr Curley and colleagues[1] found that a nurse-implemented, goal-directed sedation protocol for children undergoing mechanical ventilation for acute respiratory failure did not reduce the duration of mechanical ventilation compared with standard of care. In an accompanying Editorial, Dr Mehta[2] raised the question of whether a low adherence rate to a complex protocol (71%-100%) or a difference in administered drugs with bioaccumulation between the groups contributed to the null findings. This large randomized clinical trial of sedation using a bedside protocol in critically ill children may have been confounded by an intervention group who were younger and less sick and who received more frequent assessments.

Previous work in adult critical care has demonstrated 3 fewer days of mechanical ventilation through the use of a multidisciplinary team bundle approach to care based on an ABCDE (awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility) protocol.[3] This approach has allowed patients to be more awake to participate in early mobility and physical therapy, potentially minimizing myopathy acquired in the intensive care unit and reducing time spent receiving mechanical ventilation.

Previous work by Curley et al[4] has demonstrated that the State Behavioral Scale (SBS) has an interrater reliability score of 0.44 to 0.76 in younger patients. I question whether the authors' null findings may result from the variation between bedside nurses or between different centers because the unit of randomization was the pediatric intensive care unit (PICU). Were measures of variation between bedside nurses determined prior to the study? Was consideration given to additional measurements for level of sedation prior to the study? Also, could a high turnover of PICU nurses have led to a relatively inexperienced workforce responsible for sedation assessments? Do the authors have any further data that may offer insight into how turnover or experience may have confounded the study?

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1. Curley MA, Wypij D, Watson RS, et al; RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators Network. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA*. 2015;313(4):379-389.

2. Mehta S. Protocolized sedation in critically ill children. *JAMA*. 2015;313(4):363-364.

3. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. *Crit Care Med*. 2014;42(5):1024-1036.

4. Curley MAQ, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med*. 2006;7(2):107-114.

In Reply Dr Remy is concerned that null findings of the RESTORE clinical trial may have been the result of the cluster randomized design leading to variation in sedation assessments between bedside nurses and among different centers. Remy asks whether measures of variation between bedside nurses were determined prior to the study, whether additional sedation measures were considered, and whether nurse turnover or experience could have confounded study results.

During the RESTORE start-up phase, all PICUs implemented the SBS as a unit-based standard of care. The SBS was selected because it was the only valid and reliable sedation assessment instrument specific for intubated pediatric patients. The weighted κ scores of 0.44 to 0.76 noted by