heterogeneity in its definition. Longitudinal data would be informative with regard to whether sensitization has a role in bronchiectasis pathogenesis or the bronchiectasis state predisposes the host to atopy. The study is notable on several levels. The international collaboration is, again, remarkable. The study moves the field of bronchiectasis forward in two significant ways: first, it describes atopy and sensitization in bronchiectasis on a large, multicenter scale that has not been done before. Second, it identifies sensitization as an "endophenotype" of bronchiectasis. The need for endophenotypes in bronchiectasis was born out of failed trials that sent a painful but clear message that non-CF bronchiectasis not only is not CF but also will not behave like CF in response to therapies with proven efficacy in CF. These data may in part explain the baffling failures of large-scale therapeutic trials to demonstrate improvement in exacerbation frequency from inhaled antibiotics despite a decrease in bacterial burden. With further study, the sensitization patterns and immune profiles identified in this work will mature as guides to categorization and therapy. No doubt Mac Aogáin and colleagues have gotten off to a productive start. ■

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Author disclosures are available with the text of this article at www.atsjournals.org.

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HDL Cholesterol: A "Pathogen Lipid Sink" for Sepsis?

The lack of a specific medical therapy for sepsis, a dysregulated response to infection that is responsible for up to half of all inpatient deaths (1), plagues critical care. Numerous clinical trials have failed to improve mortality (2, 3). Furthermore, the failure of many anticytokine therapies challenges the classic paradigm of observing an association between plasma levels of a purported marker and sepsis mortality, testing the marker's causality and modifiability in animal models, and then moving toward clinical trials to test marker blockade. Correlation does not equate with causation, and strategies to modify a correlated but noncausal biomarker are unlikely to improve sepsis survival. Although controlled interventional trials provide strong evidence for causality, it is frequently unethical or impractical to randomize subjects to high- or low-biomarker infusions, leaving us to bridge this gap with observational designs. Our field needs smarter tools to dissect correlation from causality and identify the causal biomarkers of sepsis to speed the development of sepsis therapy.

Fortunately, tools to infer causality from observational data do exist. Classically, such methods have been applied to avoid making policy decisions based on biased or inconsistent association estimates (4) due to measurement error, uncontrolled confounding, or reverse causation. One potential solution is to use an instrumental variable analysis. This approach is valid if the instrument, or reliably measured variable, has a strong association with a potential mediator variable, and there is no correlation between the instrument and the outcome being studied (5). For example, if distance from a grocery store reliably predicts intake of fresh produce, then the association between grocery store distance and lean weight can be used to infer whether produce intake has a causal relationship with weight. Genetic researchers extended this approach by using genotype(s) to predict biomarkers, testing the association between biomarker-predicting genotypes and disease, and inferring whether the biomarker has a causal relationship with disease. Called Mendelian randomization (MR) analysis, this genetic instrumental variable strategy is attractive because genotypes are assigned at random by gametogenesis and genotype assignment always precedes outcome. Such MR analyses have provided evidence that low-density lipoprotein cholesterol (LDL-C) plasma concentrations are causally related to cardiovascular disease and mortality (6), whereas markers such as C reactive protein are not (7), thus focusing therapeutic efforts on modifying plasma LDL-C. Furthermore, MR has enabled the identification of novel genetic regulators of LDL-C, which has translated to a new class of lipid-lowering agents (8).

Could similar strategies be applied to identify key causal intermediates for sepsis death? In this issue of the *Journal*, Trinder

Originally Published in Press as DOI: 10.1164/rccm.201811-2084ED on November 14, 2018

and colleagues (pp. 854–862) implicate serum high-density lipoprotein cholesterol (HDL-C) as a potentially causal contributor to sepsis survival, and suggest that medications that boost HDL deserve investigation for sepsis (9). The foundation for this work was the group's prior observation that low HDL-C was a strong predictor of organ dysfunction or death among patients presenting to an emergency room with suspected sepsis (10). Because HDL-C can bind and sequester pathogen lipids, including endotoxin, patients with lower HDL-C may have worse sepsis outcomes. The authors used an astute approach to identify genetic predictors of serum HDL-C and performed an MR analysis of the effect of HDL-C on sepsis survival. First, they performed targeted resequencing of 10 HDL-C–associated genes in 200 subjects with suspected sepsis, focusing on SNPs that influence coding sequence or splicing. For each candidate gene, they tested whether subjects with low HDL-C had an excess of coding SNPs compared with subjects with normal or high HDL-C, and the gene *CETP*—encoding CETP (cholesteryl ester transfer protein)—was the only one to demonstrate an HDL-C association during sepsis. Furthermore, one missense *CETP* SNP, rs1800777, drove the association between *CETP*, HDL-C, and increased sepsis-related organ failures. The SNP seems to be a CETP gain-of-function variant, with rs1800777 carriers exhibiting higher plasma CETP activity. Because the sequencing was performed in the same 200 subjects in whom the authors first reported an association between low HDL-C and sepsis death, raising concerns about selection bias and generalizability, the authors validated that rs1800777 was associated with decreased sepsis survival in two additional sepsis populations. Finally, the authors used rs1800777 as a genetic instrument to predict a portion of HDL-C variance. By MR analysis, each log decrease in genetically predicted HDL-C during early sepsis was associated with an increase in the adjusted hazard ratio for mortality, leading to the causal inference that lower serum HDL-C during sepsis has a causal effect on reduced sepsis survival.

This study has several strengths, including its sophisticated design to test suspected functional genetic variants via a sequencing approach. By focusing on genome-wide association study–validated loci that influence HDL-C, the authors were more likely to discover a strong relationship between genotype and HDL-C, and they showed the SNP's gain-of-function action by testing plasma levels of CETP activity. The consistency of the SNP's association with both HDL-C and sepsis organ failure and survival in multiple populations lends confidence that rs1800077 is a valid genetic instrument for making a causal inference about HDL-C. Most importantly, by establishing serum HDL-C as a potential causal intermediate in sepsis survival, this study introduces HDL-C modification as a highly novel therapeutic strategy for sepsis, which is an exciting concept in that agents to inhibit CETP already exist.

Trinder and colleagues acknowledge that although their genetic instrument meets validity criteria, it is rare: only 10 of the 200 subjects in the early infection cohort carried this SNP, and small sample sizes are at risk for unstable effect estimates. However, the validation of the SNP–mortality association in additional sepsis populations is reassuring. HDL-C is less established than other potential sepsis prognostic biomarkers, and thus it will be important to ensure the consistency of this association in much larger populations. Finally, the authors acknowledge some inconsistencies in the data supporting a strategy of CETP blockade in sepsis, including worrisome observations of increased infections and excess mortality in randomized trials of one CETP inhibitor, torcetrapib, for coronary arterial disease (11). In addition, the recent disappointing results of the EUPHRATES (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock) trial, which randomized subjects with septic shock and elevated endotoxin activity assays to a hemofiltration therapy targeted at reducing endotoxin activity (12), likewise dampens enthusiasm for the notion that modifying endotoxin availability is a helpful approach in sepsis.

Although it remains to be seen whether CETP inhibition might be a viable therapeutic option in sepsis, the study by Trinder and colleagues is nonetheless a robust example of employing genomic and statistical tools in observational clinical cohorts to identify novel therapeutic targets in sepsis. Similar approaches should be embraced by investigators in our field, with dedicated attempts to replicate prior findings while generating new discoveries. The validation of causal intermediates should accelerate translation from observation to safe, testable interventions, ideally leading to improved sepsis therapy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Precision Medicine in Acute Kidney Injury: A Promising Future?

Despite increased focus over the past decade, the management of patients with acute kidney injury (AKI) remains largely supportive, including dialysis for severe cases. Clinical trials in AKI examining timing of dialysis, intensity of dialysis, pharmacotherapy, and novel biologics have been consistently negative (1–6). One postulated reason for this dearth of positive trials is the inherent delay in intervention for patients with AKI due to a reliance on serum creatinine, and researchers have embarked on a decades-long journey to identify a biomarker of AKI that would identify patients while kidney damage was actively ongoing and before serum creatinine increases. Numerous biomarkers of tubular injury have now been identified (7, 8), and in the ICU these biomarkers have modest sensitivity, specificity, and association with outcomes (9, 10). However, these biomarkers have so far failed to recategorize the heterogeneous syndrome of AKI into more clinically useful subtypes or be incorporated into clinical practice. There has been some progress with biomarkers of cell cycle arrest, most notably TIMP2*IGFBP7 (tissue inhibitor of metalloproteinase-2*insulin growth factor binding protein-7), to identify patients at high risk of AKI (11, 12). In patients after cardiac bypass surgery at high risk for AKI (as denoted by elevated TIMP2*IGFBP7), there was a lower incidence and decreased severity of AKI in patients who were randomized to a "KDIGO (Kidney Disease: Improving Global Outcomes) bundle," which included monitoring of hemodynamic parameters, avoidance of nephrotoxins, and holding angiotensin-converting-enzyme inhibitors (13). Although prevention may be possible, the role of biomarkers in guiding treatments or response to therapy remains unclear.

For this reason, the article by Bhatraju and colleagues (pp. 863–872) in this issue of the *Journal* represents meaningful progress (14). The authors applied latent class analysis to a discovery group of 794 patients admitted with systemic inflammatory response syndrome to the ICU and a replication cohort of 425 patients with acute respiratory distress syndrome (ARDS) and identified two subphenotypes of AKI (AKI-SP1 and AKI-SP2). The patients in AKI-SP2 were sicker and had worse renal function; higher rates of sepsis, ARDS, and mortality; and lower rates of renal recovery. The authors determined via least absolute shrinkage and selection operator method that the ratio of angiopoietin-1 and angiopoietin-2 (Ang1/Ang2) and sTNFR-1 (soluble tumor necrosis factor receptor-1) were sufficient to accurately distinguish between the two subphenotypes of AKI (c-statistic > 0.93).

Ang1 and Ang2 are endothelial growth factors, which both bind to the extracellular portion of the Tie-2 receptor. They have opposing actions: Ang-1 stabilizes the vascular endothelium, and Ang-2 destabilizes the vascular endothelium. Consequently, the ratio of these endothelial growth factors provides an assessment of endothelial dysfunction and is associated with prognosis in several cohorts of critically ill patients with and without AKI (15, 16).

These sophisticated statistical techniques and biomarkers determined what clinicians intuitively understand: patients with more severe inflammation do worse. The authors then reidentified the subphenotypes in a random subset of 328 patients from the VASST (Vasopressin in Septic Shock Trial) who had measurements available for Ang1/Ang2 and IL-8 (17). (Soluble tumor necrosis factor receptor-1 was not available in the VASST cohort, but IL-8 was notably different between AKI-SP1 and AKI-SP2 in the discovery and replication cohorts.) This clinical trial was a randomized, double-blind study comparing vasopressin and norepinephrine infusions to norepinephrine alone in 776 patients with septic shock. The study had shown no differences in mortality or rates of renal failure between patients in either treatment group. Once patients were recategorized into the AKI subphenotypes, patients in AKI-SP1 (the less ill group) had improved 90-day mortality with early addition of vasopressin compared with norepinephrine alone. This association persisted

Originally Published in Press as DOI: 10.1164/rccm.201810-2032ED on November 6, 2018