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Should We Tip Our CAPs to Statins?

Community-acquired pneumonia (CAP) exerts a high burden of mortality and morbidity in older patients, even when antibiotics covering the most likely pathogen(s) are appropriately prescribed. There is a pressing need to improve outcomes for this patient population. The intriguing article by Sapey and colleagues (pp. 1282–1293) in this issue of the *Journal* provides cautious optimism in this setting (1).

On the basis of the pivotal role of neutrophils in the pathogenesis of CAP, and armed with preliminary data demonstrating that statins reverse aberrant function in neutrophils from older patients with CAP, the group performed an exploratory, single-center, randomized placebo-controlled trial of simvastatin (80 mg once daily for 7 d) in 62 older patients with CAP and sepsis who were managed outside the ICU.

The authors should be commended for focusing on a patient group with real unmet clinical need, which is understudied (because such research is so challenging). They have produced tantalizing data suggesting statins can beneficially modulate key neutrophil functions associated with CAP, such as impaired chemotaxis, extracellular release of human neutrophil elastase, and the generation of neutrophil extracellular traps (NETs) in response to *in vitro* stimulation. Within the rigor of a randomized controlled trial, these consistent signals strongly suggest the observed effects of statins on neutrophil function are "real."

However, perhaps the most fascinating and clinically relevant data pertain to the significant reduction in Sequential Organ Failure Assessment score and "hospitalization-free survival" associated with simvastatin. The improvement in both hints that the (nonsignificant) reduction in mortality in the statin group deserves further study. This is supported by the acceptable safety profile, and particularly the suggestion that concomitant use of macrolides that inhibit cytochrome P450 3A4 (CYP3A4) was well tolerated.

If statins genuinely improve outcomes in older patients with CAP, are the changes in neutrophil function responsible or do they reflect improvement generated through another mechanism(s)? Although biologically plausible, there is insufficient evidence that neutrophils mediate the improvement associated with statins. The effects on neutrophil functions observed were small, and their clinical relevance is far from certain. Whether effects of statins are maintained when circulating neutrophils adhere to vascular endothelium or extravasate to enter the alveoli remains unknown. Data from other lung conditions suggest markedly different phenotypes for circulating and alveolar neutrophils (2). If an immunomodulatory effect of statins is responsible, we must keep in mind that statins influence other immune cells, particularly lymphocytes (3), and these were not studied by Sapey and colleagues (1).

A more likely explanation might lie within cardiovascular effects of statins. CAP is associated with excess major cardiovascular events, both in the short and medium term (4, 5). Periprocedural use of statins for cardiac interventions has yielded varying results (6, 7). An undefined number of patients in the trial by Sapey and colleagues (1) were taking maintenance, lower-dose statins, and statin "reloading" has been associated with beneficial outcomes after percutaneous coronary intervention (8). However, whether prior use of statins has a beneficial effect on outcomes after CAP remains contentious (9, 10), and acute use of statins for acute coronary syndrome (analogous to application in the trial considered here) does not improve outcomes (11).

The possibility remains that subtle effects on vascular tone and perfusion in key tissue beds underlie potential benefits. Statins have various positive effects on endothelial function, particularly around nitric oxide bioavailability (12, 13).

Whatever the mechanism(s) by which simvastatin appears to have improved outcomes in the study, further trials to validate these

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findings, and a large multicenter trial to examine the effects of statins in this cohort, are justified. Experience from impressive, large trials of statins in inflammatory lung disease will benefit design (14). The harder issue is what to measure as the primary outcome? Although "NETosis" was the primary outcome measure in the current study, this is ill suited to larger trials. The clinical relevance of a "change in NETs" is unknown, the difference between the groups was a fraction of the effect size used in the authors' own power calculation, the test is unlikely to have been applied at a constant point in the natural history of CAP, the assay is labor intensive, and it is not validated for use in other laboratories. The biology of NETs is complex (15), and the assay used by Sapey and colleagues involves stimulating neutrophils *ex vivo* with a concentration of bacterial formyl peptides they probably never encounter (1). The clinical variables seem far more relevant candidates for primary outcome measures in future trials. However, caution must also be exercised here, as the Sequential Organ Failure Assessment score was not designed for use outside ICUs and yields very low scores in patients with CAP managed in hospital wards, making the clinical relevance of a reduction hard to interpret. Similarly, the impressive change in hospitalization-free survival (a composite of death and readmission to the hospital) is tempered by its emergence only in *post hoc* analysis. Mortality seems the alternative of most clinical relevance, given the promising separation in the two groups.

The authors make a persuasive case for further exploration of statins for older patients with pneumonia outside the ICU. They were most unlucky that their study ended just before the Sepsis-3 guidelines emerged (16), such that the definition of sepsis they used is obsolete. Their own *post hoc* data (admittedly using very low numbers) suggested that "CAP and Sepsis-3-positivity" may not yield as good discrimination of outcomes. Furthermore, the threshold for admitting patients with CAP to the ICU varies considerably between healthcare systems. Considerations like these suggest the optimum design of future, larger trials will be complicated.

However, Sapey and colleagues have delivered an important trial combining research advocacy for older patients, greater clarity around which subgroups may benefit most from statins, evidence that neutrophil biology is affected by statins (and may be a biomarker of their effective dose), and sufficient enticing data on clinical outcomes to justify further investment in this area (1). We *should* tip our caps to this study. However, much careful thought and far more data are required before we can fling them in the air celebrating a significant new way of reducing mortality and morbidity attributable to CAP. ■

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Cardiopulmonary Impact of Hypoxic Ischemic Encephalopathy in Newborn Infants

The Emerging Role of Early Hemodynamic Assessment in Determining Adverse Neurological Outcomes

Perinatal hypoxic ischemic insults are frequently accompanied by multiorgan system involvement. Although cerebral injury is the most concerning consequence, myocardial dysfunction may also contribute to postnatal neurological impairment and exacerbate organ damage (1). The cardiovascular determinants of cellular homoeostasis rely on the distinctive interface between myocardial performance, end-organ perfusion, and tissue oxygen delivery and consumption (2). Perturbations to the cardiovascular system in infants with hypoxic ischemic encephalopathy (HIE) can include myocardial damage, right ventricular (RV) dysfunction, and altered transitional circulation (1).

The complexity of the perinatal transition poses a unique challenge for neonates with HIE, particularly when faced with acute cardiopulmonary illness. The increased recognition that cerebral autoregulation can be impaired in this population underpins the need for a comprehensive appraisal of all the determinants of cellular homeostasis. Therefore, a high index of suspicion for cardiopulmonary dysfunction is important in the neonate with clinical and biochemical evidence of a hypoxic ischemic insult (1, 3), but unfortunately, the conventional cardiovascular markers (i.e., blood pressure and heart rate) are recognized as late findings of inadequate myocardial performance to sustain appropriate organ perfusion and tissue oxygenation (2). Along with a lack of clarity regarding thresholds for hemodynamic screening and intervention, traditional parameters make it challenging to delineate the nature of cardiopulmonary instability with precision or to decipher whether compromise is a result of cardiac injury, intra- and extracardiac shunting, alterations in systemic and pulmonary vascular resistance, or a developmentally immature myocardium. Hemodynamic assessment with echocardiography enables enhanced diagnostic precision with a targeted approach to intervention that may complement a clinical examination and more accurately optimize postinsult cerebral blood flow and oxygen delivery. Although echocardiography may offer a blueprint for formulating a diagnostic impression, further investigation is needed to determine the risk/benefit ratio of treatment and the thresholds for initiating treatment (3).

In a study presented in this issue of the *Journal*, Giesinger and colleagues (pp. 1294–1305) used data from a multicenter cohort of neonates with HIE undergoing therapeutic hypothermia (TH), with cerebral hemodynamics assessed by advanced neurophysiological and cardiovascular hemodynamic monitoring systems, to study an association between the severity of cardiopulmonary dysfunction and the composite outcome of death or abnormal magnetic resonance imaging (MRI) (4). This is the largest and most comprehensive evaluation of this high-risk population. They demonstrated that the overall cohort had depressed RV systolic function and increased pulmonary pressures compared with published normative data obtained at 24 hours of age, and that markers of impaired RV performance were independently associated with abnormal basal ganglia and/or watershed injury by MRI. RV systolic parameters and pulmonary pressures normalized on follow-up echocardiography, but evidence of early increased afterload was not discriminatory of neurological outcome. Similarly, left ventricular (LV) systolic and RV and LV diastolic function parameters were also nonpredictive of poor outcome. These findings shed some light on a population of newborns with a high burden of adverse sequelae, and enhance our understanding of additional risk factors and postnatal adaptive processes that may be associated with or predictive of morbidity in infants with HIE. The authors highlight the importance of RV performance for the potential benefit of adapting a rigorous hemodynamics approach to characterize cardiac function in these infants.

This study is timely, as the ability of a cardiac dysfunction to predict the impact of hypoxic insults on neurological outcomes has been elusive, and these results may pave the way for new strategies to address the contribution of RV dysfunction to neurological injury and/or recovery. Recent studies have shown that agents that address RV function may be associated with brain recovery in animal models of HIE (5, 6). So far, two mechanisms of cardiac dysfunction have been described in neonates with a perinatal hypoxic insult: *1*) depressed LV function from the initial insult that is further exacerbated by

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