Statins and Sepsis – Scientifically Interesting but Clinically Inconsequential

Dean T. Eurich, BSP, PhD^{1,2,4} and Sumit R. Majumdar, MD, MPH, FRCPC^{1,2,3}

¹Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, Alberta, Canada; ²ACHORD, 2-040 Li Ka Shing Center, University of Alberta, Edmonton, Alberta, Canada; ³Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada; ⁴2-040 Li Ka Shing Center for Health Research Innovation, University of Alberta, Edmonton, Alberta, Canada.

J Gen Intern Med 27(3):268–9

DOI: 10.1007/s11606-011-1939-7

© Society of General Internal Medicine 2011

Community acquired pneumonia results in over a million hospitalizations per year in the United States and over 40 billion is spent managing the disease. Despite improvements in the diagnosis, risk stratification, and treatment of patients hospitalized with pneumonia, case fatality rates remain high (about 8%), particularly among those who develop severe sepsis where mortality still approaches 30%.¹ Pneumonia is, in fact, the most common cause of severe sepsis and the overall incidence of severe sepsis is steadily increasing. Indeed, only some adjunct treatments such as steroids and activated protein C have had an impact on outcomes in patients with severe sepsis.^{1,2} Thus, many agents that have (actual or perceived) influence on the systemic inflammatory response are being pursued as adjunct therapy for treatment of pneumonia and severe sepsis.

For example, the potential role of HMG-CoA reductase inhibitors [statins] has garnered increasing attention due to the putative “pleiotropic” anti-inflammatory and immunomodulatory effects of this drug class. In this issue of JGIM, the study by Rothberg et al. is the latest and largest in a series of observational studies suggesting benefits of statins in patients with infection.³ Among 121,254 patients admitted to 376 hospitals across the United States with a diagnosis of pneumonia, Rothberg et al. observed a 15% relative reduction in the odds of death [OR 0.85, 95% CI 0.79 to 0.90] for the 23,285 statin users after adjustment for comorbidities, concomitant therapies, and hospital-related factors compared to non-statin users; the absolute mortality difference was 1.8% while the adjusted difference was 0.8%, for a NNT of 123.^{3,4} Statin therapy was also

associated with reduced 30-day readmission, need for mechanical ventilation, and ICU admission. These benefits were robust to propensity-score matching, although the strengths of associations were attenuated [for mortality, OR 0.90 95%CI 0.82 to 0.99].

Of note, the effect of statins was relatively inconsistent and varied considerably based on the underlying risk of patients; in general, those at greatest risk of mortality tended to derive the least relative benefit of statin pre-treatment. For example, in analyses that categorized patients into quintiles of predicted mortality, statin treatment was associated with the largest treatment effect in the lowest risk strata [OR 0.71] and was less effective in patients with the highest predicted risk of mortality [OR 0.87]. Similarly, statin therapy was less effective in those admitted directly to the ICU [non-significant OR 0.93] and patients receiving antibiotics directed towards more virulent organisms such as *Staphylococcus aureus* or *Pseudomonas spp.* [non-significant OR 0.95]. While absolute benefits tend to vary with baseline risk in RCTs, there is no a priori reason to believe relative benefits should vary with risk suggesting to us residual confounding.

Despite the fact these authors incorporated a robust study design and used very sophisticated analytic techniques, we believe caution must still be advised in the interpretation of small (OR<3-4) and unexpected benefits of treatments derived from observational studies.⁵ Although it is possible statin pre-treatment reduced pneumonia severity, as suggested by lower rates of mechanical ventilation and less use of antibiotics directed towards *Staphylococcus aureus* and *Pseudomonas spp.*, it is also possible that statin users were inherently at lower risk for adverse events, irrespective of pneumonia severity. Patients who are prescribed preventive therapies, like statins, often have better functional status and cognition, are often more likely to engage in other health promoting behaviors (e.g., better diets, more exercise, smoking cessation, alcohol in moderation), are more likely to seek preventative services (e.g., cancer screening, immunizations, BMD testing) and are more likely to seek and adhere to other preventative drug therapies (e.g., multivitamins, aspirin) (Figure 1).⁶

Work Performed at the University of Alberta

DTE SRM have no non-financial interests that may be relevant to the submitted work

Published online December 2, 2011

Figure 1. Conceptual model explaining the healthy-user effect.

This ‘healthy-user effect’ (or its converse, ‘frailty bias’) is well recognized within both randomized controlled trials and observational studies and has been explicitly documented with statins.^{6,7} Despite often being older and having more documented comorbidities, previous studies have shown that statin users are more likely to also receive prostate-specific antigen tests, mammograms, influenza and pneumococcal vaccinations, and patients adherent to statins (specifically) have lower risk for all types of adverse events like motor vehicle accidents or workplace injuries.⁶ Although the results of Rothberg et al. are consistent with most previous studies of statin use in patients with infections, it should be noted those studies that better controlled for characteristics of the healthy-user effect have either demonstrated abolition or significant attenuation of the beneficial effects of statins on infection-related outcomes.^{1,7}

Indeed, within the study, statin users were more likely to be non-smokers and admitted from the community and were less often prescribed thiamine (a marker for heavy alcohol consumption), nutritional supplements, total parenteral nutrition, and indwelling catheters. On the other hand, statin users were more likely to receive other important preventive medications like ACE-inhibitors that reduce morbidity and mortality. Although the observed differences in any one of these characteristics between statin users and non-users may be small, collectively these differences may introduce a large degree of bias within any non-randomized study. Without better information on patients’ functional and cognitive status and health-related behaviors, we believe it is nearly impossible to disentangle the true effect of statin therapy from confounding by the healthy-user effect on mortality in non-randomized studies. This also highlights the fundamental difficulties in evaluating preventive therapies within observational studies, particularly when seeking out novel or unexpected benefits. The same issues we describe have been seen in prior studies of the many benefits of estrogen treatment in post-menopausal

women, anti-oxidant vitamins, and influenza vaccination in the elderly.

Whether the observed reduction in mortality in non-ICU patients (and ICU admission and mechanical ventilation) associated with statins was due to statistical chance, confounding by the healthy-user effect or the truth, the impact of statins on morbidity and mortality in this study was nonetheless very modest. To our knowledge, none of the systematic reviews of the statin trials has ever demonstrated a “signal” related to reductions in fatal infections or pneumonia. The study by Rothberg et al is probably as robust and convincing an examination of the “statins and sepsis [pneumonia] hypothesis” as can be undertaken without a large clinically detailed prospective cohort of pneumonia patients or subgroup analyses of the large placebo-controlled statin trials (both essentially observational studies) or conducting a randomized trial. In theory, a trial would be most definitive but likely cost-prohibitive: to identify the (adjusted) effect size on mortality in Rothberg et al’s work would require randomizing almost 20,000 patients. We, as the authors also indicate, suggest that pre-admission statins be continued during hospitalization of patients with pneumonia or infections. That said, outside of a trial, we are not enthusiastic about initiating any new medication (statin or otherwise) of unproven benefit in sick and elderly hospitalized patients based on observational data alone. Non-randomized evidence of unexpected benefits has already led us down too many wrong paths in the past and the path seems far too well trodden for our liking.

Corresponding Author: Dean T. Eurich, BSP, PhD; 2-040 Li Ka Shing Center for Health Research Innovation, University of Alberta, Edmonton, Alberta T6G 2E1, Canada (e-mail: deurich@ualberta.ca).

REFERENCES

1. Tleyjeh IM, Kashour T, Hakim FA, et al. Statins for the prevention and treatment of infections: a systematic review and meta-analysis. *Arch Intern Med*. 2009;169(18):1658–1667.
2. Sligl WI, Milner DA, Sundar S, Mphatswe W, Majumdar SR. Safety and efficacy of cortico-steroids for the treatment of septic shock: a systematic review and meta-analysis. *Clin Infect Dis*. 2009;49:93–101.
3. Rothberg M, Bigelow C, Pekow P, Lindenauer P. Association between statins given in hospital and mortality in pneumonia patients. *J Gen Intern Med*. 1-7. doi:10.1007/s11606-011-1826-2
4. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med*. 1997;126(9):712–720.
5. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet*. 2004;363(9422):1728–1731.
6. Shrank W, Patrick A, Alan Brookhart M. Healthy User and Related Biases in Observational Studies of Preventive Interventions: A Primer for Physicians. *J Gen Intern Med*. 2011;26(5):546–550.
7. Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ*. Nov 11 2006;333(7576):999