VANCOMYCIN PASTE STILL DOES NOT REDUCE THE INCIDENCE OF DEEP STERNAL WOUND INFECTION AFTER CARDIAC SURGERY

To the Editor:

Once again,^{1,2} we are obliged to respond to misinterpretation³ of our observational study of the effect of vancomycin paste on deep sternal wound infection (DSWI) in patients undergoing cardiac surgery.⁴ Lazar's critique³ is based on a meta-analysis by Kowalewski and colleagues⁵ that fails to appreciate that 2 previous studies used historical controls.^{6,7} Both source studies performed propensity matching in an attempt to account for the numerous changes in patient acuity and medical care, antibiotic prophylaxis, surgical technique, and glycemic control between the control and case periods.⁸ No amount of matching to historical controls will account for unmeasured confounders, however, nor for clinical practices that are restricted to a single period. In contrast, with concurrent controls, our study accounted for year of surgery, patient, and surgical characteristics in a detailed logistic regression that examined these and other predictors of DSWI.⁴ After accounting for these characteristics, vancomycin paste was found to have no apparent clinical or statistical benefit.

The reported meta-analysis of Kowalewski and colleagues⁵ does not account for the overall reduction in DSWI seen in clinical practices during the last 20 years. To delineate precisely the effects of practice changes and vancomycin use with time, we performed subgroup analysis on 2 periods in our cohort of more than 14,000 patients: from 2003 to 2010 and from 2011 to 2015. We did not observe a beneficial effect of vancomycin use on DSWI incidence either before 2011 (odds ratio, 1.19; 95% confidence interval, 0.75-1.88; $P = .53$) or from 2011 to 2015 (odds ratio, 1.39; 95% confidence interval, 0.49-3.93; $P = .53$).

We would like to address the criticisms of our study in both the meta-analysis⁵ and Lazar's editorial³ on a point-by-point basis. Both expressed a view that our study failed to account for differences in patient

characteristics but did not observe our adjustment for these characteristics with the use of multivariable logistic regression modeling. Lazar³ also expressed concern that we did not perform a subgroup analysis on high risk patients such as those with diabetes. To address this issue, in subsequent analyses, we similarly observed no effect of vancomycin on DSWI incidence in patients with diabetes between 2003 and 2010 (odds ratio, 1.45; 95% confidence interval, 0.72-2.92; $P = .29$), nor from 2011 to 2015 (odds ratio, 0.44; 95% confidence interval, 0.08-2.53; $P = .36$). Lazar³ further states that other high-risk patients, such as those with long-term support hardware, cardiac transplants, and current infection (such as endocarditis), should have been examined. Analysis of low-frequency events such as DSWI in these small subgroups, however, is simply underpowered and unrealistic.

Critique of the precise and standardized DSWI outcome we measured is not well founded. We used the Centers for Disease Control and Prevention surveillance period of 90 days; longer than the Society of Thoracic Surgeons period of 30 days.⁹ The Lazar³ expressed concern that we did not include 9 patients who presented with DSWI between 91 and 365 days after surgery. Even if we accept that vancomycin paste could have favorable effects far beyond its period of biologic activity, however, inclusion of these 9 patients does not alter our findings. Similarly, we did not include superficial wound infections in our analysis, because these are often treated in the community without further hospital admission or surgery, preventing accurate delineation of the diagnosis.

An important methodologic issue for meta-analysis is the effect of publication bias.¹⁰ A reduction in treatment effect size is frequently seen in later, better-conducted, larger studies, and this is a well-known observation. Although Kowalewski and colleagues⁵ in the meta-analysis provided a funnel plot to test for publication bias, interpretation of a funnel plot is problematic when only 4 studies are examined. More quantitatively, we used the "trim and fill" approach¹¹ to address the following question: What is our best estimate of the unbiased effect size of vancomycin? This approach yields an unbiased risk ratio of vancomycin of 0.57 (95% confidence interval, 0.16-2.00); this is obviously different from the risk ratio of 0.24 reported in the meta-analysis (95% confidence interval, 0.06-0.91).⁵ In summary, caution should be taken with the results and conclusions of the meta-analysis of Kowalewski and colleagues.⁵

To summarize, we once again state that "rigorous attention to perioperative antibiotic administration and glucose management are essential components to minimizing DSWI; however, vancomycin paste does not appear to provide additional prevention of DSWI."²

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should: • Include no more than 500 words of text, three authors, and five references. • Type with double-spacing. • See <http://jtcvs.ctsnetjournals.org/misc/fora.shtml> for detailed submission instructions. • Submit the letter electronically via jtcvs.editorialmanager.com. Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity to offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.

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VANCOMYCIN PASTE AND DEEP STERNAL WOUND INFECTIONS—DÉJÀ VU ALL OVER AGAIN

Reply to the Editor:

In their letter, Lander and colleagues state that they are once again obliged to respond to the misinterpretation of their observational study¹ on the effect of vancomycin paste on deep sternal wound infection (DSWI). If the methodology of their study had not been so significantly flawed, there would be no need for further explanations.

Lander and colleagues claim that our previous study on vancomycin paste relied on propensity matching to account for numerous changes in patient acuity, medical care, antibiotic prophylaxis, surgical technique, and glycemic control. This is incorrect. In 2014, my colleagues and I reported our experience with vancomycin paste.² We compared 2190 patients from December 2003 to November 2007 who did not receive vancomycin paste with 1075 patients who did receive vancomycin paste from December 2007 to August 2013. Unlike the study by Lander and colleagues,¹ there were no differences in surgical techniques used to close the sternum, in glycemic control, or in prophylactic perioperative antibiotics. The only difference in our practice was the use of vancomycin paste. Unlike the study of Lander and colleagues,¹ the patient profiles between our groups were similar. There were no statistical differences in age, sex, congestive heart failure, peripheral vascular disease, strokes, chronic obstructive pulmonary disease, renal failure, the urgency of surgery, the presence of myocardial infarction, diabetes mellitus, or the use of single versus bilateral internal thoracic arteries. Patients who received vancomycin paste did have significantly higher incidences of active smoking and endocarditis. The unadjusted outcomes without propensity matching showed that patients who received vancomycin paste had no superficial or DSWI in both patients without diabetes (0% vs 2.3%; $P < .0001$) and patients with diabetes (0% vs 3.3%; $P = .0004$). These results remained significant even after propensity matching.

This was in sharp contrast to the study by Lander and colleagues,¹ in which there were numerous changes during the course of their study from 2003 through 2015 involving perioperative antibiotics, glycemic control, and sternal wound closure techniques. Only 34.5% of their study patients actually received vancomycin paste. High-risk patients such as those with endocarditis, patients undergoing cardiac transplantation, and those requiring placement of assist devices, who stood to gain the most from vancomycin paste, were excluded from the analysis. Lander and colleagues