

Relationship of Perioperative Hyperglycemia and Postoperative Infections in Patients Who Undergo General and Vascular Surgery

Margarita Ramos, MD, MPH,* Zain Khalpey, MD, PhD,* Stuart Lipsitz, PhD,†
Jill Steinberg, RN, MPH,† Maria Theresa Panizales, RN, MSN,† Michael Zinner, MD, PhD,*
and Selwyn O. Rogers, MD, MPH†

Objective: Evaluate the association of perioperative hyperglycemia and postoperative infections (POI) in patients who had undergone general surgery.

Background: Intensive glucose control leads to less postoperative infections (POI) in critically ill surgical patients, but the relationship of hyperglycemia and POI in a general surgical population remains unknown.

Methods: A retrospective study of 995 patients who had undergone general and vascular surgery investigated the association of perioperative acute hyperglycemia and risk of 30-day POI over an 18-month period. The primary predictor of interest was postoperative glucose (POG). Bivariate analyses determined the association of each independent variable with POI. Factors significant at $P < 0.05$ were used in multivariable logistic regression models.

Results: In bivariate analyses, preoperative blood glucose ($P = 0.012$), POG ($P = 0.009$), age ($P = 0.002$), diabetes ($P = 0.04$), American Society of Anesthesia Classification (ASAC) ($P < 0.0001$), operation length ($P = 0.02$), and blood transfusions ($P = 0.02$) were significant predictors of POI. In multivariate analyses, only POG (OR = 1.3, (1.03–1.64)), ASAC (OR = 1.9, (1.31–2.83)), and emergency status (OR = 2.2, (1.21–3.80)) remained significant predictors of POI. Postoperative hyperglycemia increased the risk of POI by 30% with every 40-point increase from normoglycemia (<110 mg/dL). Longer hospitalization was also observed for patients with POG from 110 to 200 mg/dL (OR = 1.4, (1.1–1.7)) and >200 mg/dL (OR = 1.8, (1.4–2.5)).

Conclusion: The increased risk of POI and length of hospitalization posed by postoperative hyperglycemia is independent of diabetic status and needs further evaluation to assess for possible benefits of postoperative glycemetic control in patients who have undergone general surgery.

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From the *Brigham and Women's Hospital and †Brigham and Women's Hospital Center for Surgery and Public Health, Boston, Massachusetts. Reprints: Selwyn O. Rogers, MD, MPH, Brigham and Women's Hospital Center for Surgery and Public Health, 75 Francis St, Boston, MA 02115. E-mail: srogers@partners.org.

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Postoperative infections are common and often a costly surgical complication.¹ Perioperative hyperglycemia in critically ill surgery patients increases the risk of postoperative infections² and other complications.^{3,4} In that patient population, improved control of blood glucose fluxes has been shown to improve survival and decrease morbidity.^{5,6} Despite 30 million operations performed in the United States each year,⁷ the clear association between perioperative blood glucose (BG) control and postoperative complications remains ill-defined for the majority of surgery patients.

Patients are susceptible to stress-induced hyperglycemia from surgical stress, trauma, and/or critical illness, resulting in worse surgical outcomes, independent of the diabetic status of the patient.^{6,8,9} Postoperative hyperglycemia is common. Twenty-one percent to 34% of patients who undergo operations have uncontrolled BG levels (ie, >150 mg/dL), particularly in the immediate postoperative period (<72 hours).^{10,11} Diabetic patients are at greater risk for postoperative complications as compared with nondiabetic surgery patients,¹² including postoperative infections (POI).¹³ Better diabetic control in surgical patients has been shown to reduce mortality and complications.¹⁴ Furthermore, stringent glycemetic control improves infectious and other outcomes^{2,8,15} for trauma,¹⁶ cardiac,¹⁷ and critically ill⁶ nondiabetic surgery patients. Given the prevalence of stress hyperglycemia associated with surgical procedures, we hypothesized that perioperative hyperglycemia is associated with POI. We used data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database of a single tertiary care center to evaluate the risk of POI in major general and vascular patients with perioperative hyperglycemia.

METHODS

Patient Population, Case Selection, and Data Definitions

The general approach and methods of the ACS NSQIP have been previously described in detail.^{18–25} We performed a retrospective, observational study of 995 major general and vascular surgery patients at the Brigham and Women's Hospital (BWH) who were enrolled in the ACS NSQIP over an

18-month period (July 2005–December 2006) with prior approval from the Human Subjects Office at our institution. Randomization and eligibility criteria were per ACS NSQIP guidelines. The primary outcome of interest was POI, defined as the occurrence of 1 or more reports of pneumonia, wound infections, urinary tract infections, and sepsis in the first 30 days after surgery. Other outcomes measured were mortality and length of hospital stay (LOHS) within 30 days of surgery. The primary predictor of interest was POG, defined as the first 1-time BG value measured from skin closure to within 1 week after surgery.

Statistical Analysis

Analysis was performed using SAS statistical software. Wilcoxon rank sum tests were used for comparing continuous variables and “count outcome” LOHS between the 2 groups. Fisher exact test was used to determine differences in proportions between 2 groups for dichotomous and categorical variables. Multivariate logistic regression was used to determine if POG was an important predictor of the dichotomous outcome POI (yes/no), while controlling for the above potential confounders and reported in terms of odds ratios. The Akaike Information Criterion was used to determine the best fitting logistic regression model. Adjusted probabilities of complications were then calculated and plotted as a function of POG. Similarly, multivariate negative binomial regression was used to determine if POG was an important predictor of the length of stay, while controlling for the above potential confounders and reported in terms of ratios of LOHS for 2 covariate values.

RESULTS

Patient Population

The study sample had 117 (11.8%) patients with POI, whereas 878 patients had no infectious complications (NIC) during their hospital stay. The POI group was older than the NIC group, with a mean age of 61.1 ± 15 years versus 55.9 ± 16 years. The 2 groups had similar gender (POI = 63.3% female; NIC = 65.3%), race distributions (black: POI = 10.8%, NIC = 9.1%; white: POI = 88.2%, NIC = 90%), proportion of general surgery cases, length of operation, and steroid use. The POI group had higher rates of emergent cases (22.6% vs. 11%) and intraoperative blood transfusions (11.5% vs. 4.3%). There were more patients classified as ASAC III in the POI group (63% vs. 38%) and a higher proportion of ASAC II patients in the NIC group (54% vs. 32%). A greater number of patients in the POI group had pre-existing diabetes (29.7% vs. 14.1%) and used insulin (13.8% vs. 6%) before surgery. Preoperative blood glucose, POG, and WBC count were significantly higher in the group with POI (Table 1). The preoperative blood glucose values ranged from 40 to 475 mg/dL (median 96 mg/dL), whereas the range of postoperative values was 49 to 513 mg/dL (median 127 mg/dL). Of the first 1-time value of BG measurements, 84% of those without infections had BG taken in the first 24 hours, and 95% of those with infections had BG taken in the first 24 hours ($P < 0.0001$).

Postoperative Infections

Every 40 mg/dL increase in POG led to a 30% increased risk of POI, after adjustment for linear POG in a logistic model (OR = 1.3 (1.03–1.64)) as shown in Figure 1. Other models tested replicated the significant association between POG and POI (quadratic POG: $P = 0.03$ and log of POG: $P = 0.03$, not shown). Secondary predictors found to be significant in multivariable logistic regression were ASAC (OR = 1.9 (1.03–1.64)) and emergency status (OR = 2.2 (1.21–3.80)), as shown in Table 2.

Patients with POI had significantly elevated POG (142.4 ± 41.5 ; $P < 0.001$) compared with those without infections (Table 3). The POG for specific infections was significantly higher for pneumonia ($P = 0.05$) and surgical site infections ($P = 0.03$). POG was similar in those with POI and those without complications for septic shock, urinary tract infections, deep surgical site infections, and wound disruption. Of note, those patients in septic shock had POG mean of 115 mg/dL, reflecting tight glucose control in the Surgical Intensive Care Unit (SICU). This small percentage of patients with septic shock was controlled with intensive intravenous insulin protocols in the SICU. Per hospital protocol, intravenous insulin drips were not used on the wards.

Secondary Outcomes

Elevated POG levels also increased the LOHS (Table 2). When divided into quartiles (<110 mg/dL, 110–150 mg/dL, 150–200 mg/dL, >200 mg/dL), patients with BG values of 110 to 200 mg/dL had a 0.4 day longer hospital stay, and those patients above 200 mg/dL had a 0.8 extra day stay in the hospital as compared with surgery patients with POG below 110 mg/dL (data not known). Other predictors significant for greater LOHS were black race ($P = 0.008$), higher ASAC ($P < 0.001$), and emergent surgery ($P < 0.001$). Postoperative complications other than infections were also increased with higher BG levels with a mean of 144.3 ± 47.2 when compared with patients without complications ($P = 0.51$). POG was not statistically significantly elevated in those with and without the complication of mechanical ventilation >48 hours or for deaths <30 days of surgery (Table 3).

DISCUSSION

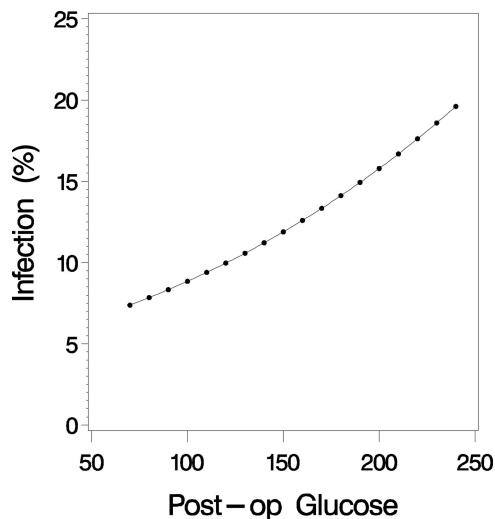
We assess the association between POG with POI in a heterogeneous general and vascular surgical population. Postoperative hyperglycemia is associated with an increased risk of 30-day postoperative infectious complications and a longer hospital stay, independent of diabetes. Demographics and clinical characteristics were adjusted using robust statistical tools. We present novel findings of a positive association between higher postoperative hyperglycemia and increased risk of POI and LOHS after general and vascular surgery that remained statistically significant, after adjustment for diabetes and other known predictors of postoperative infections.

Randomized control trials in medical, cardiac, and neurosurgical populations have found reduced rates of bacteremia,⁶ duration of antibiotic usage, infection rates²⁶ and incidence of recurrent infections²⁷ when patients have strict

TABLE 1. Demographics and Clinical Characteristics of Study Groups

Characteristic	Patients With Postoperative Infections (n = 117)	Patients With No Postoperative Infections (n = 878)	P
Age, mean ± SD	61.1 ± 15.3	55.9 ± 16	0.002
Women (%)	63.3	65.3	0.7
Race, n (%)			
Black	10 (9.1)	85 (10.8)	0.9
White	99 (90.0)	693 (88.2)	
Other	1 (0.9)	8 (1)	
Surgery and hospitalization factors, n (%)			
Emergent, n (%)	26 (22.2)	96 (11.0)	<0.001
General surgery, n (%)	70 (80.5)	484 (83.3)	0.5
Length of operation in hours, mean (SD)	3 (2)	2.6 (1.5)	0.02
ASA classification, n (%)			
I	2 (2.3)	30 (5.2)	<0.001
II	28 (32.2)	318 (54.7)	
III	55 (63.2)	220 (37.9)	
IV	2 (2.3)	13 (2.3)	
Intraop. blood transfusion (units of RBC, >2)	10 (11.5)	25 (4.3)	0.02
Comorbidities, n (%)			
Diabetes status			
No known diabetes mellitus	69 (79.3)	499 (85.9)	0.04
Oral medications	6 (6.9)	47 (8.1)	
Insulin	12 (13.8)	35 (6.0)	
Steroid use, n (%)	6 (6.9)	22 (3.8)	0.2
Laboratory values, mean ± SD			
Preop. blood glucose	11.1 ± 33.8	108.6 ± 47.5	0.012
Postop. blood glucose	142.4 ± 41.5	132.5 ± 40.3	0.009
Preop. blood WBC	9.4 ± 5.2	8.4 ± 4.4	0.02
Postop. blood WBC	11.1 ± 5.6	11.3 ± 8.0	0.9

Wilcoxon rank sum test was used as appropriate.

**FIGURE 1.** Relationship between postoperative hyperglycemia and risk of postoperative infection (POI).**TABLE 2.** Risk Factors Associated With Increased Postoperative Infections and Increased Length of Hospital Stay in Multivariate Linear Logistic Regression Analysis

Variable	Adjusted OR (95% CI)	P
Postop. infections		
Postop. blood glucose (BG)	1.3 (1.03–1.64)	0.026
10-point increase	1.07 (1.008–1.132)	
ASAC	1.9 (1.31–2.83)	0.0009
Emergent surgery	2.2 (1.21–3.80)	0.009
Increased length of hospital stay		
Postop. blood glucose (mg/dL)		
110–150	1.4 (1.1–1.7)	0.001
150–200	1.4 (1.1–1.7)	0.003
>200	1.8 (1.4–2.5)	<.0001
Black race	1.4 (1.1–1.7)	0.008
ASAC	1.6 (1.4–1.8)	<.0001
Units of blood transfusion	2.1 (0.6–1.0)	0.0005
Emergent surgery	2.2 (1.3–1.8)	0.01

ASA reported was measured as a continuous variable and got similar results when using ordinal variables for ASA.

TABLE 3. Mean Glucose Levels by Type of Postoperative Complication

Postoperative Status	Total (n)	Mean Postoperative Blood Glucose of Complication \pm SD in mg/dL	P Versus No Complication/No Death
No complication/no death	836	131.8 \pm 38.1	—
Total infectious complications	117	142.4 \pm 41.5	0.006
Sepsis	23	148.9 \pm 46.5	0.056
Septic shock	4	115.8 \pm 15.7	0.407
Pneumonia	37	141.2 \pm 35	0.049
Urinary tract infection (UTI)	16	140.7 \pm 44.6	0.453
Surgical site infection (SSI)	52	143.1 \pm 39.5	0.031
Deep SSI	3	175.3 \pm 63.8	0.114
Organ space infection	1	114	—
Wound disruption	6	157 \pm 68.3	0.564
Other complications	55	144.3 \pm 47.2	0.051
Mechanical ventilation >48 h	40	147.2 \pm 51.3	0.596
30-d mortality	22	154.1 \pm 89.2	0.194

Infectious outcomes data obtained from BWH NSQIP.

glycemic control. The Portland protocol provides parameters of BG control with a blood glucose goal of <150 mg/dL in diabetic patients undergoing cardiac surgery and has significantly reduced infections in the acute postoperative period.^{28,29} Although multiple BG control protocols exist,^{30–35} there is a paucity of clinical evidence on the effect of stress-induced hyperglycemia control on POI in diabetic and nondiabetic patients undergoing general and vascular surgery.^{2,15} The risk of POI in diabetic patients has been well described,¹¹ and control of POG has been shown to dramatically reduce wound infection rates and mortality in diabetic patients.¹⁴ However, defined parameters for postoperative hyperglycemia in nondiabetic patients has not been elucidated. This study provides a unique contribution to understanding the association of perioperative hyperglycemia and postoperative outcomes in a general and vascular surgery population.

Length of hospital stay (LOHS) was significantly increased in the group of patients with higher POG levels. Similarly, a study of strict hyperglycemic control in diabetic patients after CABG surgery found a significant reduction of postoperative LOHS, by about 3 days.²⁷ In addition, an interventional study of trauma patients reported a higher LOHS in a control group whose BG were poorly controlled.¹⁶

Our study has some important limitations. The overall incidence of POI was low and limited the analysis of an association between postoperative hyperglycemia with individual types of POI. The variety of procedures (emergent and elective) provided a broad enough case-mix to draw comparisons to other hospitals and patients, but further analysis by type of operation using billing codes or other classifications would be necessary to enhance the generalizability of this study. Our results are limited by the collection of variables in a retrospective fashion. However, the strict and comprehensive ACS NSQIP guidelines reduce the effect of misclassifi-

cation error. Residual misclassification of outcomes is still a possibility, given that the outcomes were diagnosed clinically without a priori standard diagnostic algorithms. Although important variables that account for increased risk of infections were controlled for in our multivariate analysis, such as age, gender, elective versus emergent surgery, diabetes, ASA classification, number of blood products received, and length of operation, among others, the role of body mass index (BMI) and wound classification as predictors of postoperative infections needs further exploration in the context of POG and risk of POI.

A randomized clinical trial comparing the effects of tight glucose control (<110 mg/dL) versus standard glucose management (<200 mg/dL) in patients who have undergone general and vascular in a non-ICU setting is necessary to assess causation in the association of hyperglycemia and postoperative infections. The use of a tight glucose control may also lead to a higher risk of hypoglycemia, a potential deleterious effect. In a clinical trial by Van den Bergh et al, 11.4% of those in the <110mg/dL group versus 1.8% of those with glucose control between 180 and 200 mg/dL had blood glucose <40 mg/dL. However, the mean value of hypoglycemia did not differ between the 2 groups (32 \pm 7 mg/dL conventional group and 33 \pm 5 mg/dL intensive group). Hypoglycemia sequela was similar for both groups, except for neurologic sequela, which was higher in the intensive glucose control group.³⁶ In our study, there were 13 values in the preoperative measurements and 3 postoperative measurements, which were <60 mg/dL glucose levels. There were no incidents of hypoglycemia <40 mg/dL in both preoperative and postoperative blood glucose levels, reflecting early clinical intervention of hypoglycemia. To avoid hypoglycemia in the setting of tight glycemic control, quality improvement measures, such as adequate training of glucose

management, the creation of designated teams of glucose control experts to aid the primary team in optimizing glucose monitoring and treatment, and setting parameters to alert providers early of a fall in blood glucose level before a hypoglycemic event, are some measures that could decrease or even eliminate the risk of hyperglycemia.

CONCLUSION

Patients who had undergone general and vascular surgery with postoperative hyperglycemia have an increased risk of 30-day POI and a longer hospital stay, independent of preoperative BG levels or diabetic status. Further research is needed to characterize the etiology of hyperglycemia in POI, and the possible role of intensive glucose control in such patients to decrease the risk of postoperative infectious complications. Postoperative glycemic control could be a simple, actionable intervention to decrease the risk of postoperative infectious complications after noncardiac surgery.

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Discussions

DR. HIRAM C. POLK, JR. (LOUISVILLE, KENTUCKY): I have a question for Dr. Rogers. How did you choose the 995 patients? Are they consecutive? Are they all yours, and were there any exclusions?

Our own in vitro work in this field concentrated on modified antigen presentation (Turina M, Fry DE, Polk HC. Acute hyperglycemia and the innate immune system: clinical, cellular and molecular aspects. *Crit Care Med*. 2005;33(7):1624–1633); and it always bothered me that it required a relatively large dose of LPS and a wide variation in glucose, value 400, to accomplish some of the changes you talked about. The idea that you could see the scales up to as little as 40 mg/dL is really remarkable, and I hope it is also reproducible.

It is also fascinating, according to the results from our current prospective study in some smaller hospitals, that hypothermia is being avoided and monitored in nearly 98% of cases in these hospitals. On the other hand, clinicians have missed the boat when it comes to hyperglycemia. Nearly a third of all patients with diabetes are not monitored for intraoperative glucose during long surgical procedures and, interestingly enough, 29% of people with very high glucose in the holding area before operation are not monitored.

Finally, I would like you to comment on the finding that a 40 mg/dL increase in glucose raises your infection rate by 30%. If that could be shown in some large trials or databases like UHC, you could change some thinking about this for the better.

DR. JOHN M. DALY (PHILADELPHIA, PENNSYLVANIA): Americans have seen a substantial increase in their body mass index and the incidence and prevalence of obesity. We recently reviewed a cohort of trauma patients prospectively and correlated body mass index and obesity with obesity defined as a body mass index above 30 and hyperglycemia (defined as a level greater than 200 mg/dL), age, gender, trauma index, and the types of variables that you studied. Both hyperglycemia and body mass index significantly correlated with infectious complications and lead independently to infections. Mortality was similar in these patients, but infectious complications were clearly related to both obesity and hyperglycemia. Did you measure body mass index and were there any correlations with hyperglycemia and the occurrence of complications?

DR. ORLANDO C. KIRTON (HARTFORD, CONNECTICUT): I have several questions. First, I saw a significant association of postoperative infections with ASA classification, and ASA

classification can be viewed as a surrogate for high-risk populations for adverse events. I would like you to comment on that.

Was hyperglycemia a 1-time measure or was it based on trend data? Do you support monitoring glucose levels intraoperatively? I am sure that glucose is measured in all of the preoperative patients.

DR. DANA K. ANDERSEN (BALTIMORE, MARYLAND): AS Dr. Polk suggests, there are still those who are unconvinced of this important relationship.

To address the issue of causality, I would ask if you examined those patients in your cohort who received therapy for hyperglycemia and who actually achieved successful tight glucose control. Did you see a reduction in the number of infections in those patients whose glucose levels were reduced by therapy compared with those who were not?

Finally, your abstract suggests a definition of 180 mg/dL as the goal for “stringent glucose control.” I would suggest that that is a less than stringent goal for tight glycaemic control. Others have used a goal of 150 or 120 mg/dL for a significant reduction in the infection rate, and obviously any reduction will have some benefit in reducing the infection rate.

My final question for you is, what are you doing at Brigham? Are you using continuous glucose monitors, a dedicated diabetes management team, or some other special protocol?

DR. MURRAY F. BRENNAN (NEW YORK, NEW YORK): I have a question and a comment. In addition to the BMI, did you measure steroid use?

The comment, before we get too enthusiastic about the euglycemia, based on what you did at your institution and the Joslin Clinic 30 years ago, the euglycemic clamp requires a person to receive exogenous glucose and preferably amino acids to get the favorable hyperinsulinemic events you are looking for.

DR. E. PATCHEN DELLINGER (SEATTLE, WASHINGTON): Earlier work from Vanderbilt showed that half of all hyperglycemic patients were not diabetic in their cardiac group, and I wonder if you looked at that aspect in your work. Did you observe hyperglycemia in nondiabetics, and did it increase risk in those patients and patients with diabetes? Glucose is one of the few factors that seem to have an influence on SSI rate after the operation. Antibiotics, temperature, oxygen, duration of operation, transfusion, all have their maximum effect in the operating room, whereas numerous articles in cardiac surgery show that hyperglycemia within 48 hours after the operation influences infection risk. You told us that you took the glucose closest to the end of the operation. Have you looked at any hyperglycemia within a

certain time period and can you tell us what the actual time periods of your glucose determinations were?

DR. SELWYN O. ROGERS, JR. (BOSTON, MASSACHUSETTS): With respect to Dr. Polk, we used consecutive patients whose glucose levels were obtained preoperatively and postoperatively. Analogous to your studies in Kentucky, one third of our postoperative patients did not have any glucose levels checked. Clearly, this is a potentially significant opportunity for quality improvement. Even at Brigham, we have an opportunity for quality improvement.

Once someone reaches an abnormal glucose, there is a tendency to chase it, and I think that is a useful practice. With respect to expansion of this type of study in the UHC, I think that is a very valuable next step.

Dr. Daly's comment regarding BMI is an interesting one. We did not include BMI in our data analysis. It is likely that there is a colinear relationships, although they may also be independent and worthy of analysis.

In the United States, we do have an epidemic of diabetes. I must stress that these findings were also significantly important in the nondiabetic postoperatively stressed patient.

Regarding Dr. Kirton's comment about ASA and high-risk surgery, these were general surgery and vascular surgery patients of whom a fleeting minority ended up in the intensive care unit. These data are reflective of a general and vascular surgical population who develop postoperative infections. I would suggest that this likely represents the same patient populations that all of you see every day in non-ICU settings. If there is a complication like an anastomotic leak, do these patients end up in the intensive care unit for more aggressive monitoring?

Glucose in our study was a 1-time measure. We currently do not have the data to answer that question, although it is food for further study.

Regarding the patients' preoperative glucose levels, we found that in patients who had preoperative glucose, preoperative hyperglycemia was not a statistically independent predictor of postoperative infections. Hence, in both patients with diabetes and nondiabetics, the preoperative glucose level in multivariate analysis was not significant, which argues potentially that the postoperative phase was probably the most important with respect to its effect on postoperative infectious complications in general and superficial site infec-

tions, in particular. As noted throughout the United States, about a quarter of all postoperative infections are of the SSI variety. If we can impact the rate of SSIs, we may significantly improve the quality of our surgical services.

Regarding Dr. Andersen's comment, I do take it under advisement that this is not a causality study and that was indicated as a limitation in our conclusions. At this point, we did not undertake an analysis to investigate therapeutic interventions in response to high glucose levels postoperatively.

I will note that for patients with elevated serum glucose levels in the postoperative period, there was a seemingly dose-dependent effect with each increment of 40 mg/dL with an increased risk of postoperative infection so that strongly argues for a biologic plausibility behind the observation.

Further work is needed to determine causality. Another question asked about dedicated diabetes teams. I think we have seen a spread of practices develop in the ICU. The residents are exposed to the tight insulin therapy in the intensive care unit and, therefore, often think about hyperglycemia when they are on the wards as well.

We do have dedicated diabetes teams that interface with the surgical services, particularly for the management of patients who are diabetic. Occasionally, they see patients in the postoperative state who are not diabetic or are potentially prediabetic who have elevated glucose levels.

Interestingly, in the cardiac surgical literature, for patients who were diabetic who were exposed to the Portland protocol and had their glucose levels controlled, those patients with lower glucose levels experienced lower rates of postoperative infections, particularly mediastinitis, compared with nondiabetic patients, arguing again for the "biologic plausibility" of these observations.

As for the question about steroid use, there was no statistically significant difference in steroid utilization in our general surgical and vascular surgical patients, and it was not an independent predictor of postoperative infectious outcomes.

The final question asked when glucose was checked. This was an observational study, and glucose was checked within 7 days of the index operation. Specifically, for every one of our patients who developed a postoperative infection, there was a glucose measurement within 68 hours of the index operation. This led us to consider a quality improvement initiative within our own institution making postoperative glucose checks part of our routine postoperative management.