Intraoperative management and the risk of surgical site infections after general and vascular surgery: a report from the Multicenter Perioperative Outcomes Group

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Introduction

Over 40 million major operative procedures are performed in the US annually.(1) Despite decades of research, perioperative mortality and morbidity remain a major healthcare system cost and detriment to long-term quality of life. Specifically, healthcare associated infections (HAI) in surgical patients present an overwhelming public health and cost burden. Approximately 3 to 5% of operations are complicated by a surgical site infection (SSI), translating to 500,000 to 1 million patients affected annually. Ref## The preventable costs associated with each SSI range from $2,000 to $130,000, depending upon the surgical procedure and SSI location. Ref## The significant impact of SSI, public scrutiny, and Center for Medicare and Medicaid Services pay-for-reporting initiatives have driven most facilities to achieve 95% compliance with the current SSI prevention bundle supported by the National Quality Forum. Ref##

Despite compliance with these measures, detailed surgical registries continue to demonstrate SSI rates of 3 to 5%, leaving policy makers, payors, providers, and patients seeking more data to establish the effectiveness of these measures.Ref## Concurrently, intraoperative anesthetic management has been implicated as a modifier of long term outcomes reaching beyond traditional cardiopulmonary events. The role of intraoperative blood pressure, vasopressor administration, prophylactic antibiotic re-dosing, prophylactic antibiotic weight-based dosing, aggressive normothermia, and fluid resuscitation on the risk of SSI remains unclear.

In this study, we sought to identify the impact of anesthetic management variation on surgical site infections. Using the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) data collection methodology, we integrated

prospectively collected risk adjustment and outcome data with intraoperative anesthesia electronic health record (EHR) data across four US medical centers. Our primary hypothesis is that intraoperative hypotension or significant vasopressor administration may be associated with an increased risk of SSI. Our secondary hypothesis is that appropriate antibiotic re-dosing and weight based dosing would decrease the risk of SSI.

Materials and Methods

Institutional review board approval was been obtained for this multicenter, prospective observational study (University of Michigan, Ann Arbor Michigan). Because no care interventions were involved and all protected health information was removed prior to data analysis, patient consent was waived. The ACS-NSQIP methodology has been described in detail elsewhere and will be briefly reviewed in this manuscript.Ref##

Patient population

A systematic sampling process is used to select cases for data collection and analysis. At the studied institutions (University of Michigan, OHSU, Columbia University, and Massachusetts General Hospital), general and vascular operations requiring general, epidural, spinal, or peripheral nerve blockade anesthesia are prospectively divided into 8-day cycles. The first 40 operations within each 8-day cycle are included. High volume, low risk operations such as inguinal hernia repair or breast lumpectomies are limited to five operations in 8-day cycle to provide a broad operative procedure sampling. Patients with specific preoperative conditions that may confound the analysis of SSI risk factors will be excluded using ACS-NSQIP defined elements: emergency surgery, open wound with or without infection, current pneumonia, acute renal failure 24 hours prior to surgery, transfusion of 4 or more units of packed red blood cells within 72 hour prior to surgery, preoperative sepsis or systemic inflammatory response syndrome within 48 hours prior to surgery, ventilator dependence within 48 hours of surgery, coma, paraplegia, quadriplegia, or prior operation within 30 days.

Using primary CPT code, patients undergoing burn debridement or skin grafting as a primary procedure will also be excluded.

Primary and secondary outcome

The primary outcome will be a composite SSI outcome definition: superficial incisional SSI, deep incisional SSI, organ / space SSI, or wound disruption. Secondary outcomes will be clinically significant deep incisional or organ / space SSI.

ACS-NSQIP independent variables

The following ACS-NSQIP preoperative clinical variables will be evaluated for a relationship to intraoperative management techniques or the occurrence of a SSI itself: age, male sex, body mass index, diabetes mellitus, current smoker within 1 year, alcohol consumption of 2 or more drinks per day in the two weeks prior to admission, severe COPD, congestive heart failure within 30 days, myocardial infarction within 6 months, previous coronary intervention or cardiac surgery, angina within 30 days, hypertension, history of revascularization for peripheral vascular disease, ongoing dialysis requirements, transient ischemic attacks, or stroke, disseminated cancer, loss of 10% of body weight in 6 months, steroid use for a chronic condition, chemotherapy within 30 days, and ASA physical status. Age will be transformed into a categorical variable with deciles of age with a reference age range of 18-40. Body mass index will be transformed into categorical variables based upon the World Health Organization classification scheme (< 20, 20-25, 25-30, 30-35, 35-40, 40-50, and > 50 kg/m^2). ASA physical status

will be transformed into three categorical dummy variables: ASA 1 or 2, 3 or 4, and 5. Diabetes mellitus will be transformed into two dummy variables: diabetes mellitus requiring oral hypoglycemic treatment without insulin, and diabetes mellitus requiring insulin treatment with or without oral hypoglycemics. A single dummy variable expressing the procedure's inherent risk of surgical site infection will be used to adjust for operative risk.Ref## {Raval, 2010 #128}

Anesthesia EHR independent domains

Hemodynamics

Intraoperative hemodynamic monitoring data were acquired via automated, validated electronic interface from the physiologic monitors for each center's anesthesia EHR. The interface records one invasive arterial catheter blood pressure measurement each minute and all non-invasive blood pressure measurements. Each intraoperative anesthesia record was analyzed as a series of 10 minute periods. For each 10 minute period, the median systolic blood pressure (SBP), median mean arterial pressure (MAP), and median heart rate (HR) were calculated. Clinically aberrant values defined as a SBP > 280 mmHg, SBP < 50, MAP > 200 mmHg, MAP < 40, or HR < 30 beats per minute were excluded from the median calculation. The use of a median value and exclusion of aberrant values has been demonstrated to decrease the impact of monitoring artifacts and clinically transient physiologic derangement. These median values were compared to absolute and relative hypotension thresholds, SBP < 80, SBP < 70, MAP < 60, MAP < 50, SBP 30% decrease from preoperative baseline, SBP 40% decrease, MAP 30%

decrease, and MAP 40% decrease. If a patient exceeded a given threshold, they were noted to have experienced that specific level of hypotension.

The total number of vasopressor boluses was calculated as a number of "equipotent" doses: phenylephrine (100 mcg), ephedrine (5 mg), and epinephrine (10 mcg) and will be reported as a continuous variable. Administration of a vasopressor infusion (phenylephrine, norepinephrine, dopamine, epinephrine) was a separate clinical data element analyzed as a Boolean variable.

Fluid balance

The total fluid balance was calculated for each case. Total intraoperative fluids and blood products administered were calculated separately to the nearest milliliter, as were urine output, estimated blood loss, and other outputs. In instances where blood products are documented as units instead of mL, an approximate volume equivalent for that product was used.

Fluid Balance Additions		
Fluid type	Data element in MPOG database	Conversion Factor to Crystalloid Equivalents
Crystalloid fluid	Total milliliters of crystalloid fluid administered	1:1
Colloid fluid	Total milliliters of colloid fluid administered	2:1
Packed red blood cells	# of units of packed red blood cells administered × 350 ml / unit	3:1
Fresh frozen plasma	# of units of fresh frozen plasma administered × 350 ml / unit	3:1
Platelets	# of units of platelets administered x 50 ml/unit	3:1
Cryoprecipitate	# of units of cryoprecipitate administered x 50 ml/unit	3:1

Fluid Balance Subtractions		
Estimated blood loss	Milliliters of blood loss observed by clinical team	3:1
Urine output	Milliliters of urine output collected by anesthesiologist during operative period	1:1
Other fluid outputs	Ascites drainage, gastric tube drainage, fluid loss from surgical drains	2:1

Prophylactic antibiotic optimization

Given that timely administration of prophylactic antibiotics is commonly observed with > 95% compliance at participating centers, there is inadequate variation to offer analytical value. However, the redosing of antibiotics and dosage adjustment for patients > 80 kg remain controversial and variable.Ref## For all procedures, a Boolean variable evaluating whether dosage was increased for patient with a weight > 80 kg will be calculated. The following definitions of weight based dosing for these patients will be: cefazolin 2 gm, vancomycin 1.5 gm, cefoxitin 2 gm, clindamycin 900 mg, levofloxacin 750 mg, ampicillin / sulbactam 3 gm, cefepime 2 gm, metronidazole 500 mg, and gentamicin 2 mg/kg. In addition, for procedures with a surgical duration > 3 hours, redosing of antibiotics within 3 hours of initial administration will be evaluated as a Boolean variable. Redosing of metronidazole, gentamicin, vancomycin, levofloxacin, and ceftriazone will not be evaluated due to their long half-lives.Ref##

Aggressive normothermia

Although current surgical care improvement guidelines evaluate normothermia as a simple Boolean concept at arrival in the PACU, patients undergoing major general and vascular surgery may be exposed to harmful intraoperative hypothermia that is unmeasured by this simplistic performance metric. In addition, there are conflicting data regarding the value of normothermia, with some studies indicating that normothermia may increase the risk of infection.Ref## To evaluate this intraoperative management component, each case will be divided into a 10-minute epochs and the median core-body temperature will be calculated for each epoch. These data will be used to create two continuous variables. First, the nadir temperature for each case will be used as an independent variable. Second, the number of epochs < 35.0 C, < 35.5 C, and < 36.0 C will be calculated for each case.

Statistical analysis

Statistical analysis will be performed using STATA SE version 12 (STATACORP LP, College Station, TX).. Univariate analyzes will be performed using Pearson Chi-Square, Fisher's Exact Test, Student's t-test, and Mann Whitney U Test as appropriate for all preoperative and intraoperative variables for the primary outcome. Odds ratios and 95% confidence intervals will be reported and a p-value <0.05 will be considered statistically significant.

Prior to building any models, all covariates will be analyzed for collinearity using the condition index. If any condition indexes are ≥ 30, a bivariate correlation matrix will be constructed to evaluate pair-wise correlations. [20] Groups of variables with a pair-wise correlation ≥ 0.70 are deemed to demonstrate high levels of collinearity and will be

addressed by one of two options: collapsing the two variables into a single concept or removing one of the two variables from the models.

As stated previously, the primary outcome will be a composite SSI outcome definition: superficial incisional SSI, deep incisional SSI, organ / space SSI, or wound disruption. The secondary outcome will be the clinically significant deep incisional or organ / space SSI. For both the primary and secondary outcomes, four distinct models to evaluate each intraoperative management domain will be performed: hemodynamic management, fluid balance, antibiotic optimization, and aggressive normothermia. Each of the component variables within that management domain will be combined with the ACS-NSQIP preoperative and operative variables. In addition, each model will also include the surgical complexity score that was calculated based on the principal CPT code.

Since this study involves a multi-center approach, a clustered logistic regression will be used using the xtgee command in STATA. The family will be set as binomial (due to the dichotomous outcome) with an exchangeable correlation matrix and the clustering variable will be the individual institutional site identification number set as a fixed effect. All variables deemed to be significant ($p < 0.05$) are established as independent predictors within each specific domain. Each variable is also assessed for effect size using adjusted odds ratios and 95% confidence intervals comparing the likelihood of SSI among patients with and without the risk factor. [23] Model diagnostics will be performed to assess model stability.

Finally, an overall model incorporating all four domains, preoperative and operative ACS-NSQIP variables, and the surgical complexity score will be performed using the same methodology described above.

Power analysis:

Although this is an observational analysis that does not involve recruitment of patients, a power analysis to establish that the database is capable of detecting a statistically significant difference is important. Previous SSI prevention interventions such as normothermia, antibiotic prophylaxis, and chlorhexidine surgical prep have demonstrated relative risk reduction rates ranging from 40% to 70%.Ref## For purposes of this power analysis, we will assume a conservative benefit of only 20% for each of the intraoperative interventions, or the group as a "bundle." Review of national ACS-NSQIP data demonstrates a composite SSI rate of 5.8%. A 20% relative risk reduction would result in an observed SSI rate of 4.6%. A two group continuity corrected $\chi 2$ test with a 0.050 two-sided significance level will have 80% power to detect the difference between these two rates when the sample size in each group is 5539, resulting in a total sample size of 11,078. In aggregate, the four institutions presented in this proposal already offer 30,000 ACS-NSQIP cases with integrated anesthesia EHR data.

Limitations / Questions

- Is this project too big and looking at too many things?
    - Should it be broken up into several papers
- Should we include emergency procedures?
- Should we restrict to colectomies only?
- Should we try to evaluate anesthesia technique (or epidural use)?
- Should we include FiO2 or depth of anesthesia