PCRC Proposal Cover Sheet

Title of Study or Project:	The role of perioperative antibiotics and the risk of surgical site infections after general and vascular surgery: a report from the Multicenter Perioperative Outcomes Group
Primary Institution:	Yale School of Medicine
Principal Investigator:	Robert B. Schonberger
Co-Investigators:	Amit Bardia, Kevin Schuster, Feng Dai, Sachin Kheterpal, Leif Saager
Type of Study:	☒ Retrospective Observational ☐ Exploratory
IRB Number/Status:	Will obtain approval from Yale IRB
Hypothesis:	We propose to test the hypothesis that timely antibiotic dosing, redosing, weight-based dose adjustments in accordance with guidelines, and appropriate timing of infusions to ensure completion of administration prior to skin incision will be associated with a lower incidence of SSIs. In a parallel analysis, we propose to describe the patterns of antibiotic prophylaxis (dosing, redosing, and timing) found across MPOG institutions.
Number of Patients/Participants:	All adult patients who underwent non-cardiac surgery documented in the MPOG database.
Power Analysis:	Review of literature demonstrates a composite SSI incidence of about 4%. A 20% relative reduction would result in an observed SSI rate of 3.2%. Assuming the rate of "appropriate antibiotic usage" is 92%, a $\chi 2$test with a 0.050 two-sided significance level will have 80% power to detect the difference between these two rates when a total sample size is 55,637
Proposed statistical test/analysis:	Univariate analyses will be performed to investigate the association of all preoperative and intraoperative variables with the primary outcome. Clustered or mixed-effects logistic regression models will be developed to associate the SSI outcome with each component of intraoperative antibiotic management domain. Random effects for hospitals and anesthesia providers will be included to address the clustering of different surgical cases.
Resources (Brief summary of resources):	MPOG programmer to pull the data. Analysis to be done by Yale School of Medicine statistician within the Yale Center for Analytical Sciences (supported in part by CTSA Grant UL1 RR024139 from the National Center for Advancing Translational Sciences (NCATS).

The role of perioperative antibiotics and the risk of surgical site infections after general and vascular surgery: A report from the Multicenter Perioperative Outcomes Group

Introduction

Prevention of surgical site infection (SSI) continues to be a major challenge for the health care system since it incurs a substantial toll on public health and significantly inflates health care cost. SSI is now the leading cause of health care related infection, complicating about 2-5 % of all surgeries(1-3). It affects about 125,000 cases annually accounting for nearly a million excess hospital days and just under $1.6 billion in additional health care costs(4). It is estimated that half of the SSIs are preventable(5) and not surprisingly, the prevention of health care-associated infections has been a priority objective of the U.S. Department of Health and Human Services (HHS)(6) over the past several years. Public reporting of SSI outcomes is now mandatory and reimbursement for management of SSIs is being reduced or denied(7,8) in an effort to curb its incidence.

Despite the institution of stringent measures and surveillance programs, surgical registries continue to show SSI rates of about 2-5%(9,10) and SSIs remain a key cause of prolonged hospitalization, morbidity and death. The continued health care burden caused by SSI calls for closer scrutiny of the current clinical practices especially pertaining to perioperative antibiotic coverage. Although the institution of timely perioperative antibiotic prophylaxis is now a National Quality Anesthesia Care Measure(11), much remains to be known about antibiotic redosing, weight based adjustments and completion of antibiotic infusion prior to skin incision(7).

In this study, we seek to describe current practice of antibiotic prophylaxis among MPOG institutions, and in the subset of MPOG centers contributing NSQIP data, to identify the effect of appropriate perioperative antimicrobial coverage – specifically regarding timing, dose adjustments, and redosing - on SSI. We propose to utilize the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) data collection methodology, and to integrate these prospectively collected risk adjustment and outcome data from 6 centers within MPOG with intraoperative anesthesia electronic health record (EHR) data available across more than 50 medical centers within MPOG. Beyond our descriptive aim to describe current practice, our primary inferential hypothesis is that timely antibiotic redosing, weight based dose adjustments in accordance with guidelines, and appropriate timing of infusions to ensure completion of administration prior to skin incision will each be associated with a lower incidence of SSIs while controlling for common confounders available within the MPOG and NSQIP datasets.

Methods

We will seek approval from the Yale IRB for this multicenter, observational retrospective study. Data have previously been collected under an umbrella IRB protocol within the University of Michigan. The ACS-NSQIP methodology has been described in detail elsewhere(12).

Patient population

All patients equal or greater than 18 years of age undergoing non-emergent non-cardiac surgical procedures involving a skin incision will be included in the study. Patients with conditions that could confound the analysis of SSI risk factors including emergency surgery, open wound with or without infection, current active infection, ongoing preoperative antibiotic therapy, missing perioperative antibiotic/medication documentation, ventilator dependence within 48 hours of surgery, or prior operation within 30 days; will be excluded. A complete list of the exclusion criteria from ACS-NSQIP variables is documented in Supplement 1.

Covariates / Confounders:

The following MPOG and ACS-NSQIP preoperative clinical variables will be evaluated for a relationship to intraoperative management techniques or the occurrence of a SSI itself and will be controlled for as potential confounders in the primary inferential analyses: age, male sex, body mass index, diabetes mellitus, current smoker within 1 year (NSQIP), severe COPD (NSQIP), congestive heart failure within 30 days (NSQIP), history of myocardial infarction, hypertension, history of peripheral vascular disease, ongoing dialysis requirements (NSQIP), transient ischemic attacks or stroke (NSQIP),

disseminated cancer (NSQIP), loss of 10% of body weight in 6 months (NSQIP), steroid use for a chronic condition (NSQIP), chemotherapy within 30 days (NSQIP), and ASA physical status.

Intraoperative variables including hypotension, hypothermia, transfusion volume, the need for vasopressor / inotrope infusion, and surgery duration will be included.

Body mass index will be transformed into categorical variables based upon the clinically relevant 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.

For intraoperative variables, hypotension will be calculated as the time in minutes below MAP 55mmHg. Intraoperative hypothermia will be calculated as a sum of areas under the curve for temperature < 36 (i.e. the sum of the time-temperature integrals of temperature less than 36 degrees Celsius using 36 as the baseline). Transfusion volume will be calculated as the number of pRBC units transfused between surgery start and surgery end. The need for infusions of vasopressors and/or inotropes will be coded as yes/no based on the intraoperative anesthetic record. Duration of surgery will be calculated as the period of time from incision to surgery end.

<u>Endpoints:</u>

The primary end point to which we will attempt to associate antibiotic prophylaxis will be occurrence of a NSQIP-adjudicated SSI during the period from 2011 to 2018. SSIs will be a composite of superficial (only skin or subcutaneous tissue of the incision), deep (deep soft tissues), and organ space (any part of the anatomy other than the incision, which has been opened and manipulated during the operation), as provided by the NSQIP.

Appropriate antibiotic prophylaxis:

Definition for appropriate antibiotic prophylaxis will be used per the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS) and American Society of Health-System Pharmacists (ASHP) guidelines(13). The appropriate redosing interval, weight-based adjustment and infusion rate criteria are shown in Supplement 2. Data on timing, dose, and redose of antibiotics will be obtained from MPOG.

Statistical analysis

Statistical analysis will be performed using SAS version 9.4 (Cary, NC). A two-sided p-value <0.05 will be considered statistically significant, if not otherwise noted. Descriptive statistics (means, medians, frequencies) will be used to characterize demographics and all extracted clinical variables. Histograms and box plots will be constructed to evaluate distributions of continuous variables and identify potential outliers. Each outlier will be reviewed carefully and verified. Categorical items with more than two categories that do not exhibit sufficient variability across response levels will be dichotomized.

For the primary inferential aim, univariate analyses will be performed using Pearson Chi-Square, Fisher's Exact Test, Student's t-test, and Mann Whitney U Test as appropriate

to investigate the association of all preoperative and intraoperative variables with the outcome of NSQIP-adjudicated SSI.

In addition to examining the prevalence or patterns of SSI by different center or surgery types, three distinct clustered or mixed-effects logistic regression models to will be developed using SAS GLIMMIX procedure to associate the SSI outcome with each component of intraoperative antibiotic management domain: redosing interval, weight-based adjustment, and infusion time criteria. Specifically, we propose to test the hypothesis that timely antibiotic dosing, redosing, weight-based dose adjustments in accordance with guidelines, and appropriate timing of infusions to ensure completion of administration prior to skin incision will be associated with a lower incidence of SSIs while controlling for significant confounders. Random effects for hospitals and anesthesia providers will be included to address the clustering of different surgical cases. We will examine the modification effects of other specific factors, adding them into the model as fixed factors, which include patient level demographics such as age, health of patient (ASA class), BMI, gender, race/ethnicity, and ACS-NSQIP preoperative and operative variables.

Generally, only the factors with $p \leq 0.1$ from univariate analysis will be included in the multivariable regression model. Clinical variables with shown evidences affecting the risk of SSI will also be included in the model. For example, each model will also include the surgical complexity score that was calculated based on the principal CPT code. Collinearity, the linear assumption, and the additivity assumption of the predictors will be checked, and nonlinear modeling of continuous predictors (e.g., infusion time) will be investigated. If necessary, highly correlated groups of predictors will be examined and

dimensionality will be reduced either by subject matter knowledge (i.e., principal components), or by simple point scores.

The amount of variability in the SSI outcome that is explained by the final prediction model will be quantified by the adjusted-R^2 statistic or C-statistics (i.e. AUC). and the Hosmer-Lemeshow goodness-of-fit (GOF) test will be used to check if the final model fits the data well. A GOF P-value > 0.05 will indicate that a model is a good fit or well-calibrated. In addition to p-values for independent variables in the final models, as the measures of effect sizes, we will also report adjusted odds ratios and 95% confidence intervals comparing the likelihood of SSI among patients with and without the risk factor.

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

For the descriptive aim in parallel with the above analysis, practice patterns across MPOG institutions in relation to antibiotic dosing, redosing, and timing will be examined. The distribution of adherence to these practices will be examined, and patient, provider, and institution level predictors of adherence to these practices, individually and as a bundle will be examined.

Power analysis:

Although this is an observational analysis that does not involve recruitment of patients, a power analysis to establish that the database can detect 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%. 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 literature demonstrates a composite SSI incidence of about 4%. A 20% relative reduction would result in an observed SSI rate of 3.2%. Assuming the rate of “appropriate antibiotic usage” is 92%, a $\chi 2$ test with a 0.050 two-sided significance level will have 80% power to detect the difference between these two rates when a total sample size is 55,637. In aggregate, the institutions presented in this proposal already offer sufficient ACS-NSQIP cases with integrated anesthesia EHR data.

References:

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11. NQMC Anesthesia Care Measure https://www.asahq.org/quality-and-practice-management/quality-and-regulatory-affairs/quality-reporting-programs/nqmc-anesthesia-care-measures. 2015.
12. Pandey A, Sood A, Sammon JD et al. Effect of preoperative angina pectoris on cardiac outcomes in patients with previous myocardial infarction undergoing major noncardiac surgery (data from ACS-NSQIP). Am J Cardiol 2015;115:1080-4.
13. Bratzler DW, Dellinger EP, Olsen KM et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195-283.

Supplement 1: Exclusion criteria

Serial Number	NSQIP Exclusion Criteria
1	Emergency surgery
2	Open wound with or without infection
3	Current active infection
4	Transfusion of 4 or more units of packed red blood cells during surgery
5	Preoperative sepsis or systemic inflammatory response syndrome within 48 hours prior to surgery
6	Ventilator dependence within 48 hours of surgery
7	Coma, paraplegia, quadriplegia
8	Surgery within preceding 30 days
9	Ongoing preoperative antibiotic therapy
10	Missing perioperative antibiotic/medication documentation

Supplement 2: Suggested initial dose and time to redosing for antimicrobial drugs commonly utilized for surgical prophylaxis.

Antibiotics	Standard Dose	Initiation of infusion prior to skin incision (minutes)	Weight-based dose Adjustment	Recommended redosing interval (hours)
Ampicillin-Sulbactam	3g	60		2
Ampicillin	2g	60		2
Aztreonam	2g	60		4
Cefazolin	2g	60	3gm for patients >120kg	4
Cefuroxime	1.5 g	60		4
Cefotaxime	1g	60	2gm recommended in obese patients	3
Cefoxitin	2g	60		2
Cefotetan	2g	60		6
Ceftriaxone	2g	60		NA
Ciprofloxacin	400mg	120		NA
Clindamycin	900mg	60		6
Ertapenem	1g	60		NA
Fluconazole	400mg	60		NA
Gentamycin	5mg/kg based on dosing weight*	60		NA
Levofloxacin	500 mg	60		NA
Metronidazole	500 mg	60		NA
Moxifloxacin	400mg	120		NA
Piperacillin-Tazobactam	3.375g	60		2hrs
Vancomycin	15mg/kg	120		NA

* If patient's actual weight is more than 20% above ideal body weight (IBW), the calculation for dosing weight (DW) is DW = IBW + 0.4(actual weight – IBW).