Is It Time to Refine? An Exploration and Simulation of Optimal Antibiotic Timing in General Surgery

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BACKGROUND: Postoperative infections increase morbidity, resource use, and costs. Our objective was to examine whether within guideline recommendations an optimal time exists for an initial dose of antibiotic to reduce postoperative infections in general surgery, and to simulate the magnitude of a reduction in infections should an optimal time be implemented.

STUDY DESIGN: The population consisted of 6,731 patients who underwent 7,095 general surgery procedures between January 5, 2006 and June 25, 2012. Patients with pre-existing infections, such as pneumonia and sepsis, and patients with no recorded use of antibiotics were excluded, as were patients on vancomycin and surgical procedures longer than 4 hours in duration. The final analysis dataset included 4,453 patients. The National Surgical Quality Improvement Program was used for perioperative variables and outcomes. The end point was a composite of wound disruption; superficial, deep, organ space, surgical site infections; and sepsis. Semiparametric logistic regression was used to study the association between antibiotic timing and infection.

RESULTS: There were 444 (10%) patients with a primary end point of infectious complication. A nonlinear "bowl-shaped" relationship between duration of interval from antibiotic administration and surgical incision and infection was observed; lowest risk corresponding to administration time close to incision was 4 minutes before incision (95% one-sided CI, 0–18 minutes). The model suggested optimal timing would result in an 11.3% reduction in the primary infection end point.

CONCLUSIONS: Risk of infectious complications decreased as antibiotic administration moved closer to incision time. These data suggest an opportunity to reduce infections by 11.3% by targeting initial antibiotic administration closer to incision. (J Am Coll Surg 2013;217:628–635. © 2013 by the American College of Surgeons)

Infectious complications after surgery are ranked as the second most common type of health care–associated infection[1,2] and are linked to longer hospital length of stay, higher costs, increased hospital readmission rates, and greater mortality.[3] In the operative setting, the advisory statement from the National Surgical Infection Prevention Project recommends prophylactic antibiotics be administered within 60 minutes before surgical incision.[4] However, within this time frame, the optimal timing for prophylaxis relative to skin incision remains unclear, suggesting an opportunity to refine the guideline.

Our objectives were to examine whether within guideline recommendations an optimal time exists for an initial dose of antibiotic to reduce postoperative infections in general surgery and to simulate the magnitude of reduction in infections should an optimal time be implemented.

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METHODS

Patient population

The population consisted of 6,731 patients who underwent 7,095 general surgery procedures between January 5, 2006 and June 25, 2012. The analysis dataset included 4,453 patients with exclusions as defined in Figure 1 and characteristics as shown in Table 1. We excluded cases

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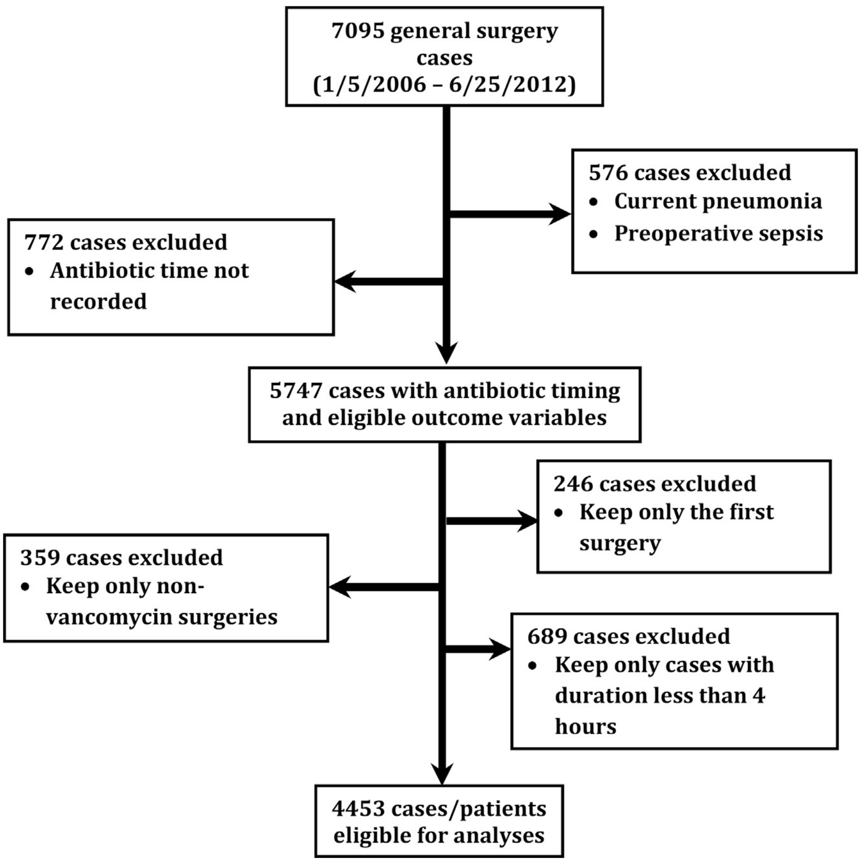

Figure 1. Consort-style diagram of the patient population.

with pre-existing infections, such as pneumonia and sepsis, and those with no recorded use of antibiotics. We included only the first operation if multiple operations were recorded in the same patient and excluded patients on vancomycin and surgical procedures longer than 4 hours in duration. Antibiotics used >5% of the time included cefazolin (49.8%), an ampicillin-based agent (27.6%), ceftizoxime (5.9%), metronidazole (5.5%), and ciprofloxacin (5.5%). Of 4,453 operation, 1,130 (25.38%) used more than one kind of antibiotic.

Data sources

Our data source for baseline variables and postoperative infection outcomes was the NSQIP. The National Surgical Quality Improvement Program is administered by the American College of Surgeons with data collected by trained registry staff using a standardized template. The NSQIP is an IRB-approved registry for research. The choices of antibiotic and intraoperative timing of administration were recorded in the electronic anesthesia record. Earlier work at our institution using Six Sigma methodology reported success with use of the electronic anesthesia record as a tool to monitor process improvement for perioperative antibiotic timing prophylaxis.[5] The choice of antibiotic was determined by the staff surgeon for individual surgical procedures in compliance with Centers for Disease Control and Prevention guidelines. Antibiotic timing was calculated as the time from antibiotic initiation to surgical incision, as recorded in the electronic anesthesia record. Antibiotics were redosed according to individual antibiotic pharmacokinetics; of note, an automated notification indicator flag alerted the provider as part of the electronic anesthesia record when another dose was indicated. Automated electronic alerts are effective in improving timely prophylactic antibiotic administration and with re-dosing.[6,7] We had IRB approval with a waiver of informed consent for this investigation.

End points

The primary end point was a composite of infectious outcomes consisting of postoperative wound disruption, superficial and deep surgical site infection (SSI), organ space SSI, and sepsis (Table 1). Definitions of these

Table 1. Descriptive Statistics of the 4,453 Patients in the Analysis

Variables	Descriptive statistics
Demographics, median (25th percentile, 75th percentile)	
Age, y	54 (42, 65)
Body mass index	28 (24, 34)
Preoperative laboratory results, median (25th percentile, 75th percentile)	
Albumin, g/dL	4.1 (4.0, 4.4)
Hematocrit, %	40.4 (37.4, 43.2)
Comorbidity, n (%)	
Diabetes	645 (14.5)
Smoking	721 (16.2)
Emergency case	188 (4.2)
Steroid use	439 (9.9)
Dialysis	42 (0.94)
Earlier operation	69 (1.6)
History of COPD	114 (2.6)
ASA classification, n (%)	
1 No ASA/unknown/no disturbance	164 (3.7)
2 Mild disturbance	1,950 (43.8)
3 Severe disturbance	2,141 (48.1)
4 Life threatening/moribund	198 (4.5)
Procedures, n (%)	
Colorectal and open abdominal procedures	2,245 (50.4)
Laparoscopic procedures	1,264 (28.4)
Assortment of hernia repairs	428 (10.0)
Breast and gynecologic surgery	354 (7.95)
Thyroid and parathyroid surgery	54 (1.2)
Miscellaneous	108 (2.4)
Antibiotic use, median (25th percentile, 75th percentile)	
Time of the first antibiotics administration (min before [−] or after [+] incision)	−19 (−30, −11)
Postoperative infections, n (%)	
Superficial incisional SSI	208 (4.7)
Deep SSI	36 (0.81)
Organ space SSI	116 (2.6)
Wound disruption	19 (0.43)
Systemic sepsis	228 (5.1)
Composite end point of SSI, wound disruption, and sepsis	444 (10)

ASA, American Society of Anesthesiologists; SSI, surgical site infection.

outcomes variables can be found at the NSQIP website (http://site.acsnsqip.org/). Postoperative complications were identified from postoperative days 1 to 30 and assigned to the postoperative day on which they occurred. In-hospital complications were identified from the hospital medical record. Complications occurring after hospital discharge up to postoperative day 30 were identified from the complete follow-up required of NSQIP. In this dataset, follow-up was >96% and included encounter documentation, mailed surveys, and telephone contact with the patient.

Antibiotic use and timing

Throughout this investigation, we focused on the time of first antibiotic dose administration only. The observed antibiotic timing was expressed as the minutes before the time of incision (time 0). If the antibiotics were administered before incision (96.9% of the cases), the antibiotic timing was recorded as a negative number; otherwise it was positive. In 1.8% of the cases, the first administration of antibiotics occurred more than 1 hour before incision, and in 3.1% of cases, administration commenced after surgical incision (Fig. 2).

Statistical methods

Characteristics of the study population were summarized by descriptive statistics. Median and 25th and 75th percentiles were used for continuous variables, and frequency and percentage were used for categorical variables. We used a semi-parametric logistic regression model to study the association between antibiotic timing, patient characteristics, and probability of infection after surgery. The effect of antibiotic timing on the outcomes was allowed to be a smooth curve with no shape restrictions. The lowest point on the estimated curve corresponded to an optimal antibiotic timing that corresponds to the lowest risk of infection. A nomogram, which graphically displays the adjusted relationship between antibiotic timing and risk of infection with all other covariates in the model fixed at certain values, was used to illustrate the results from the model. From this model, we calculated the predicted probability of infection for each patient using their patient characteristics, but a hypothetical antibiotic timing at the optimal value. The summation of individual predicted probabilities across all patients is the expected number of infections in that patient population had the optimal timing been used. This result was compared with the observed number of infections among the patients to show the benefits of the optimal antibiotic timing scheme.

To assess the magnitude of uncertainty in the estimated optimal timing, we created 1,500 bootstrap datasets by randomly sampling the patients in the study population with replacement. Each dataset was separately analyzed by logistic regression and the optimal antibiotic timing was identified. The bootstrap distribution of the optimal timing represents the approximate sampling distribution

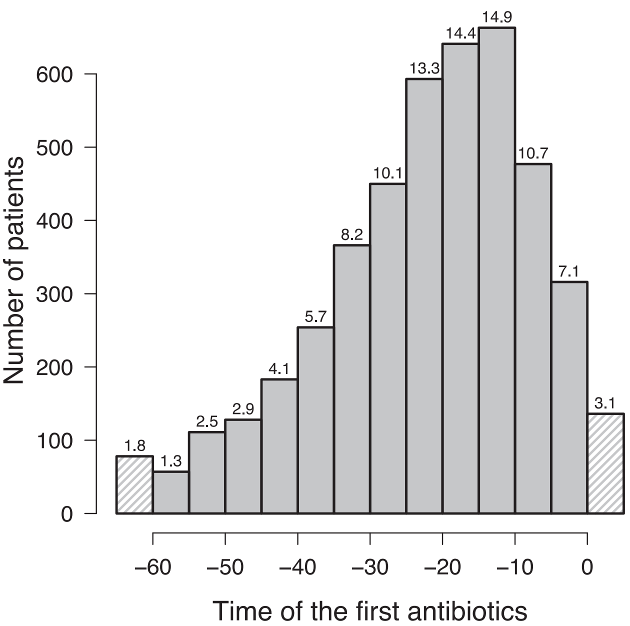

Figure 2. Distribution of time of the first antibiotic administration. Time is expressed as minutes before incision time (time zero). The number on top of each bar represents the percent of patients in that antibiotic time interval. The shaded bars on the 2 sides represent patients with antibiotic timing at least 60 minutes before incision or after the incision.

of the estimated optimal timing. Because the optimal recommended timing is before incision, we used the 5% quantile of the bootstrapped optimal timing as the one-sided 95% confidence limit for the estimated optimal timing.

R 2.12.2 software (R) was used for the statistical analyses.

RESULTS

Antibiotic timing

Of the 4,453 patients, 78 (1.8%) received prophylactic antibiotics more than 60 minutes before skin incision and 136 (3.1%) after skin incision; 4,239 (95.1%) patients received antibiotics within the 60-minute guideline. Often (70.5%) they were administered within 30 minutes of incision (Fig. 2).

Antibiotic timing and postoperative infection

Of the 4,453 patients, a total of 607 postoperative infections developed in 444 patients (10%) (Table 1). Among the 3,140 (70.5%) patients who received a pre-incision dose of antibiotic within 30 minutes before incision, 284 (9%) had infections. Among the 1,099 (24.7%) patients who received antibiotic between 30 and 60 minutes before incision, 129 (11.7%) had infections. The difference in infection rates between these 2 groups is statistically significant ($p = 0.01$). Among the 214 (4.9%) patients outside guideline recommendations, 31 (14.5%) had the composite infection outcomes.

We found a significant nonlinear relationship between antibiotic timing and risk of infection ($p = 0.012$), which is illustrated in Figure 3A as a "bowl-shaped" curve, with the lowest risk corresponding to a time close to incision (Table 2). Figure 3B translates this nonlinear relationship into the domain of expected number of infections. The optimal antibiotic timing for minimizing infection was 4 minutes before incision (one-sided 95% bootstrap CI, 0−18 minutes before incision). Had the antibiotic been routinely administered 4 minutes before incision, we predicted an 11.3 % reduction in comparison with the 444 observed number in this patient population.

Consequences of infection

Resource use was increased in patients with postoperative infectious complications. Overall postoperative hospital length of stay (surgery date to discharge date) for patients with postoperative infectious complications was a median of 7 days (quartile 1: 4 days, quartile 3: 12 days). For patients without postoperative infectious complications, postoperative length of stay was a median of 3 days (quartile 1: 1 day, quartile 3: 5 days; $p < 0.001$, Wilcoxon rank sum test).

DISCUSSION

Lord Lister's original description of the antiseptic principle in the practice of surgery suggested one could avoid the "evils" of local inflammation and infection with use of "antiseptic treatment."[8] Although our understanding and recommendations have certainly advanced, postoperative infectious complications have continued to confound physicians and contribute to increased resource use and patient morbidity.[3,9-11]

Our investigation explored the risk spectrum for postoperative infectious complications and the relationship to timing of antibiotic administration. With simulation of an optimal time, we found an opportunity to reduce postoperative infectious complications by 11.3% if the antibiotic was administered within 18 minutes of incision. In addition, considering length of stay estimates for patients with and without postoperative infectious complications (median 8 days vs 3 days; quartile 3: 14 days vs 6 days, respectively), we found considerable opportunity for reduction in resource use and cost.

Our findings confirmed those of Steinberg and colleagues[12] that moving initial antibiotic administration closer to incision time reduces postoperative infections. In their investigation, infection risk increased incrementally as first antibiotic administration to incision time increased; infection risk for administration within 30 minutes of

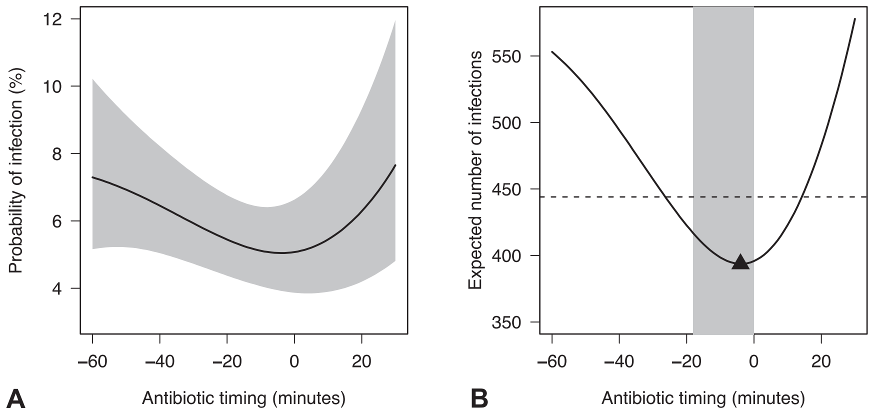

Figure 3. Illustrating the adjusted relationship between antibiotic timing and risk of composite infection outcomes based on the model in Table 2. (A) Model predicted probability of infection vs antibiotic timing, expressed as minutes before incision, based on a hypothetical nonsmoking, 54-year-old patient with a body mass index of 28, albumin 4.1 g/dL, hematocrit 40.4%, no diabetes, no smoking, no emergent surgery, no steroid use, no dialysis, no colorectal or open abdominal procedure, no earlier operation, no history of COPD, and American Society of Anesthesiologists classification of 2. The shaded area is the point-wise 95% CI of the probability curve. (B) Relationship between the antibiotic timing and the expected number of infections among the 4,453 patients according to the model in Table 2. Dashed horizontal line is the observed number of infection cases (n = 444) among those patients. At the optimal antibiotic time (solid triangle, 4 minutes before incision), the model predicts an 11.3% reduction in the number of surgical site infections, wound disruption, and sepsis. The shaded area represents the 95% one-sided CI for the optimal antibiotic time, −18 to 0 minutes.

incision was 1.6% compared with 2.4% associated with administration between 31 and 60 minutes. The authors noted that current guidelines were not designed to determine optimal timing of the initial antibiotic dose.[12]

In the cardiac surgical setting, we reported an optimal risk-adjusted antibiotic administration time had the potential to reduce infections by 9% to 31%, depending on patient risk factors and specific antibiotic administered. We similarly demonstrated the bowl-shaped relationship between timing and risk for postoperative infections, with the lowest risk being closer to incision time.[13]

Ho and colleagues examined antibiotic regimens and initial timing of prophylaxis in relationship to SSI after elective abdominal colorectal surgery.[14] Initial dose timing was considered proper if completed within 30 minutes before incision. The authors reported that 12.6% of patients had a superficial or deep incisional SSI and 8.9% had organ space SSI. Among a number of findings, administration of the initial prophylaxis dose more than 30 minutes before incision was associated with a greater likelihood of postoperative infections developing (odds ratio = 1.725; 95% confidence limits, 1.147, 2.596).[14]

Contrary to our findings, Weber and colleagues reported significantly higher risk for SSI when antibiotic administration (single-dose administration of cefuroxime) time was less than 30 minutes and 120 to 160 minutes as compared with 59 to 30 minutes before incision.[15] Of note, infection rates outside guideline recommendations (ie, administration time 60 to 74 minutes before incision) were associated with a lower rate of infection (3.4%) compared with guideline compliance times of 0 to 14 minutes and 15 to 29 minutes before incision. In addition, administration time of 0 to 14 minutes before incision had a lower rate of infection (4.69%) compared with 15 to 19 minutes before incision (6.83%). Our patient population was larger and had a higher infection rate compared with their investigation. When we analyzed our data using their data analysis plan of artificially dichotomizing groupings, our findings to recommend antibiotic administration time closer to incision time remained unchanged.

Pharmacologic properties of antibiotics with shorter administration times have dosing intervals of 3 to 6 hours, depending on the individual antibiotic. One would expect sufficient intraoperative minimal inhibitory concentrations even when antibiotics were administered 60 to 120 minutes before incision, yet a number of investigations report similar findings of substantial trends in increasing infectious risk when administration time is too early, that is, more than 60 minutes before incision.[12,15-17] It is unclear why the nature of administration

Table 2. Semi-Parametric Logistic Regression on Composite Infection Outcomes

	Composite infection outcomes	
Patient characteristics	**Log odds ratio (CI)**	**p Value**
Intercept	−2.9 (−4.2 to −1.5)	<0.001
Demographics		
Age, y	0.014 (0.0067 to 0.021)	<0.001
Body mass index	0.0026 (−0.0090 to 0.014)	0.66
Preoperative laboratory results		
Albumin, g/dL	−0.33 (−0.56 to −0.10)	0.0042
Hematocrit, %	0.0011 (−0.023 to 0.025)	0.92
Comorbidity		
Diabetes	0.044 (−0.25 to 0.34)	0.76
Smoking	0.24 (−0.021 to 0.51)	0.071
Emergency case	0.45 (0.032 to 0.88)	0.035
Steroid use	0.47 (0.16 to 0.77)	0.0026
Dialysis	−0.035 (−1.1 to 1.1)	0.95
Colorectal and open abdominal procedures	0.80 (0.59 to 1.00)	<0.001
Earlier operation	−0.95 (−1.9 to 0.032)	0.058
History of COPD	0.23 (−0.31 to 0.77)	0.41
ASA classification		
1 No ASA/unknown/no disturbance	0	
2 Mild to moderate disturbance	0.54 (−0.24 to 1.3)	0.18
3 Severe disturbance	0.52 (−0.28 to 1.3)	0.2
4 Life threatening	0.74 (−0.16 to 1.6)	0.11
Antibiotic timing,* min	See Figure 3	0.012

*The effect of antibiotic timing is modeled nonparametrically as a curve, as illustrated in Figure 3.
ASA, American Society of Anesthesiologists.

time beyond 60 minutes is associated with substantial increases in infectious complications when minimum inhibitory concentrations should be sufficient and redosing occurs at proper intervals.

One investigation that attempted to address this question offered the following potential explanations for increased infectious risk—associated antibiotic administration within more than 60 minutes of incision: antibiotic tissue levels could be too low at the time of incision, or tissue levels are too low during a later phase of the surgical intervention.[15] Our findings demonstrating the lowest rate for infectious complications with antibiotic administration time closer to time of incision suggest that perhaps blood levels of antibiotic at the time of skin incision might be of greater importance than tissue levels.

Clinical implications

In addition to a number of perioperative factors,[18-20] inadequate antibiotic prophylaxis increases the risk for postoperative infections. Publications on compliance with current guideline recommendations of antibiotic prophylaxis emphasize the importance of guideline compliance to reduce infectious complications.[4,21] Our data would suggest that simple compliance can be optimized to decrease infectious complications. In our investigation, risk of postoperative infections decreased as initial antibiotic administration time moved closer to the surgical incision. Based on our findings, it is reasonable to suggest that antibiotics be initiated closer to the surgical incision, that is, within 18 minutes of incision with 95% confidence. Consistent with other reports, our findings confirmed that administration of antibiotics more than 60 minutes before incision or after incision was associated with higher infection risk.[22-24]

Some investigators have asked whether a “plateau” has been reached in our attempt to lower SSI rates with surgical antisepsis and antimicrobial prophylaxis.[25] A recent randomized controlled trial incorporating multiple interventions to reduce infection (eg, perioperative warming, elimination of mechanical bowel preparation, intravenous fluid restriction, perioperative supplemental oxygen, and surgical wound protector) into a single treatment bundle was ineffective at reducing infection rates. Overall SSI rate was 45% in the extended (treatment) arm and 24% in the standard arm; a 2.49 increased risk in the extended arm ($p = 0.003$).[26]

Investigations on antibiotic timing consistently display a bowl-shaped relationship of timing and infection risk; however, studies vary on where the nadir risk lies in relationship to surgical incision. Of note, we never reach a nadir of zero risk for postoperative infectious complications. Although on a national level, there remains room for perfect compliance with guideline recommendations, our data and others suggest it is time to consider refinement of guidelines to do better not only to improve morbidity outcomes but also to reduce costs. Estimates of excess direct costs of hospitalization attributable to SSIs alone is $3,089, and if a second hospitalization is necessary, total direct costs attributable to treatment of infectious complications is estimated at $5,038.[3] Others have suggested that costs attributable to care of postoperative infection are increased by 2-fold compared with those without such complications.[27]

Limitations

Our investigation was an observational study with limitations inherent to observational study designs. We can only account for variables collected with the NSQIP database. We assumed that the times of antibiotic administration and skin incision as recorded within the electronic anesthesia record were accurate. Standard quality-improvement initiatives thought to influence infection risk (eg, clipping not shaving, use of skin preparation, and patient warming) were initiated per institutional quality efforts during the time of the investigation. However, as noted by others,[12] these initiatives would be expected to lower overall infection rates rather than influence antibiotic timing and infection outcomes. We did not include patients who received vancomycin prophylaxis, therefore, our findings cannot be extrapolated to include these patients.

CONCLUSIONS

The value proposition in health care is to provide efficient and safe care at low cost with good outcomes. Although current antibiotic administration guidelines are based on simplicity and rough cutoffs, there might be substantial opportunity to refine antibiotic timing to reduce postoperative infections. Our analysis suggests that there is an opportunity to improve on the current guideline metric in the setting of general surgical patients. Our work confirms the bowl-shaped relationship of antibiotic timing and infection risk and emphasizes the need for additional prospective investigation, given the potential to reduce infections by 11.3% when an optimal time is implemented.

Author Contributions

Study conception and design: Koch, Li, Hixson, Tang, Gordon, Phillips, Blackstone, Henderson

Acquisition of data: Li, Hixson, Tang

Analysis and interpretation of data: Koch, Li, Hixson, Tang, Gordon, Longworth, Blackstone, Henderson

Drafting of manuscript: Koch, Li, Hixson, Tang, Gordon, Longworth, Phillips, Blackstone, Henderson

Critical revision: Koch, Li, Hixson, Gordon, Longworth, Phillips, Blackstone, Henderson

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