World J Surg (2019) 43:2420–2425
https://doi.org/10.1007/s00268-019-05075-y

ORIGINAL SCIENTIFIC REPORT

Antimicrobial Prophylaxis Redosing Reduces Surgical Site Infection Risk in Prolonged Duration Surgery Irrespective of Its Timing

Daniela Bertschi[1] · Walter P. Weber[2] · Jasmin Zeindler[2] · Daniel Stekhoven[3] · Robert Mechera[2] · Lilian Salm[4] · Marco Kralijevic[2] · Savas D. Soysal[2] · Marco von Strauss[4] · Edin Mujagic[2] · Walter R. Marti[4]

Published online: 10 July 2019

Abstract

Background Long-duration surgery requires repeated administration of antimicrobial prophylaxis (amp). Amp "redosing" reduces incidence of surgical site infections (SSI) but is frequently omitted. Clinical relevance of redosing timing needs to be investigated. Here, we evaluated the effects of compliance with amp redosing and its timing on SSI incidence in prolonged duration surgery.

Methods Data from >9000 patients undergoing visceral, trauma, or vascular surgery with elective or emergency treatment in two tertiary referral Swiss hospitals were analyzed. All patients had to receive amp preoperatively and redosing, if indicated. Antibiotics used were cefuroxime (1.5 or 3 g, if weight >80 kg), or cefuroxime and metronidazole (1.5 and 0.5 g, or 3 and 1 g doses, if weight >80 kg). Alternatively, in cases of known or suspected allergies, vancomycin (1 g), gentamicin (4 mg/Kg), and metronidazole or clindamycin (300 mg) with or without ciprofloxacin (400 mg) were used. Association of defined parameters, including wound class, ASA scores, and duration of operation, with SSI incidence was explored.

Results In the whole cohort, SSI incidence significantly correlated with duration of surgery ($\rho = 0.73$, $p = 0.031$). In 593 patients undergoing >240 min long interventions, duration of surgery was the only parameter significantly ($p < 0.001$) associated with increased SSI risk, whereas wound class, ASA scores, treatment areas, and emergency versus elective hospital entry were not. Redosing significantly reduced SSI incidence as shown by multivariate analysis (OR 0.60, 95% CI 0.37–0.96, $p = 0.034$), but exact timing had no significant impact.

Conclusions Long-duration surgery associates with higher SSI incidence. Irrespective of its exact timing, amp redosing significantly decreases SSI risk.

Introduction

Surgical site infections (SSI) represent a major cause of postsurgical morbidity and mortality [1, 2].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-019-05075-y) contains supplementary material, which is available to authorized users.

✉ Walter R. Marti
Walter.R.Marti@hin.ch

[1] Department of Visceral Surgery, Kantonsspital Chur, Chur, Switzerland

[2] Department of General Surgery, University Hospital Basel, Basel, Switzerland

[3] NEXUS Personalized Health Technologies, ETH Zurich, Zurich, Switzerland

[4] Department of Visceral Surgery, Kantonsspital Aarau, Chirurgieaarau, Bahnhofstrasse 24, 5000 Aarau, Switzerland

Antimicrobial prophylaxis (amp) is widely recommended [3, 4], and specific guidelines have been issued by different surgical societies. However, despite adoption of measures to improve it, compliance with established protocols remains poor [5–10], and noncompliance is frequently unreported [11].

A critical aspect of amp is represented by the timing of antibiotic administration [12–14], of particular relevance in prolonged duration surgical procedures, typically characterized by increased SSI risk [15]. In these cases, repeated antibiotic administration, usually referred to as redosing, is recommended [16–18]. Lack of redosing is associated with increased SSI incidence in long-duration surgery [19–21] and represents the most frequent cause of noncompliance with established amp protocols [22]. However, impact of redosing timing has not been investigated in detail.

In previous reports, we analyzed the role of amp timing in prospective and randomized studies [23, 24], and we envisaged measures potentially contributing to decrease SSI incidence [25, 26].

Here, we have investigated the role of timing of amp redosing on SSI risk in patients undergoing prolonged duration surgery.

Patients and methods

Patient population and data collection

All patients over 18 years old consecutively undergoing abdominal, vascular, or trauma surgery over a four-year period at the University Hospital of Basel (USB) and at the Kantonsspital Aarau (KSA), two tertiary referral Swiss hospitals, were initially evaluated, irrespective of inclusion in other clinical studies [24]. Wound classes were defined according to CDC guidelines [27], and patients were classified according to American Society of Anesthesiologists (ASA) Physical Status Classification [28].

Electronic records were used to determine if amp had been given, which antibiotic had been utilized, whether redosing had been administered, and its timing.

Antimicrobial prophylaxis and redosing

All patients included in the study had to receive amp preoperatively, and redosing, if indicated. Antibiotics used throughout the study were cefuroxime (1.5 or 3 g, if weight >80 kg), or cefuroxime and metronidazole (1.5 and 0.5 g, or 3 and 1 g doses, if weight >80 kg). In cases of known or suspected allergies to these antibiotics, vancomycin (1 g), gentamicin (4 mg/Kg), and metronidazole or clindamycin (300 mg) with or without ciprofloxacin (400 mg) were used as alternative treatments.

Local standard operating procedures called for initial amp administration 1–120 min before incision. As previously recommended [2–4, 7–9], in our study, the "correct" time window for redosing started at 120 min after initiation of surgery and ended at 240 min, corresponding to one to two half-lives of the antibiotics utilized. If administered before 120 min, redosing was considered too early, whereas after 240 min it was considered too late.

Statistical analysis

Univariate tests in the descriptive statistics were performed using Chi-squared tests for nominal variables and Kruskal–Wallis tests for continuous variables. Exact Fisher's tests for data allowing direct computation of odds ratios and corresponding 95% confidence intervals were used to compare compliance regarding initial amp and redosing timing.

Multivariate testing was performed using logistic regression, with overall SSI as response. Model selection was done using AIC and likelihood ratio tests. The multivariate model was diagnosed for potential violations of model assumptions such as linearity, multicollinearity, and influential observations.

All analyses were made 3.5.0 [29], using RStudio 1.0.143.

Results

Duration of surgery is associated with SSI incidence

A total of 11,458 patients, treated in two different tertiary Swiss hospitals, were included in the study. Amp was initially administered to 9680 of them (84.4%). To minimize confounding effects of preoperatively infected wounds and clinical conditions associated "per se," to high risk of infection, we excluded from our analysis patients with class IV wounds and ASA scores of 4–5. Therefore, SSI incidence was evaluated in a total of 9045 patients with class I–III wounds and ASA scores of 1–3. Data on duration of surgery were available for 9037 of these patients.

In this large cohort of patients, we observed a significant correlation between duration of surgery and SSI incidence (ρ = 0,73, p = 0.031). In particular, a group of patients undergoing surgical procedures with >240 min duration (n = 593) were characterized by the highest SSI rate (16% of cases, Fig. 1).

A majority of these patients (n = 368/593, 62.05%) were male, and in a majority of cases (n = 338/593, 57%), visceral surgery was performed. Details on surgical interventions are reported in supplementary Table 1. Most patients were classified as ASA 2 or 3 (n = 267/593, 45%,

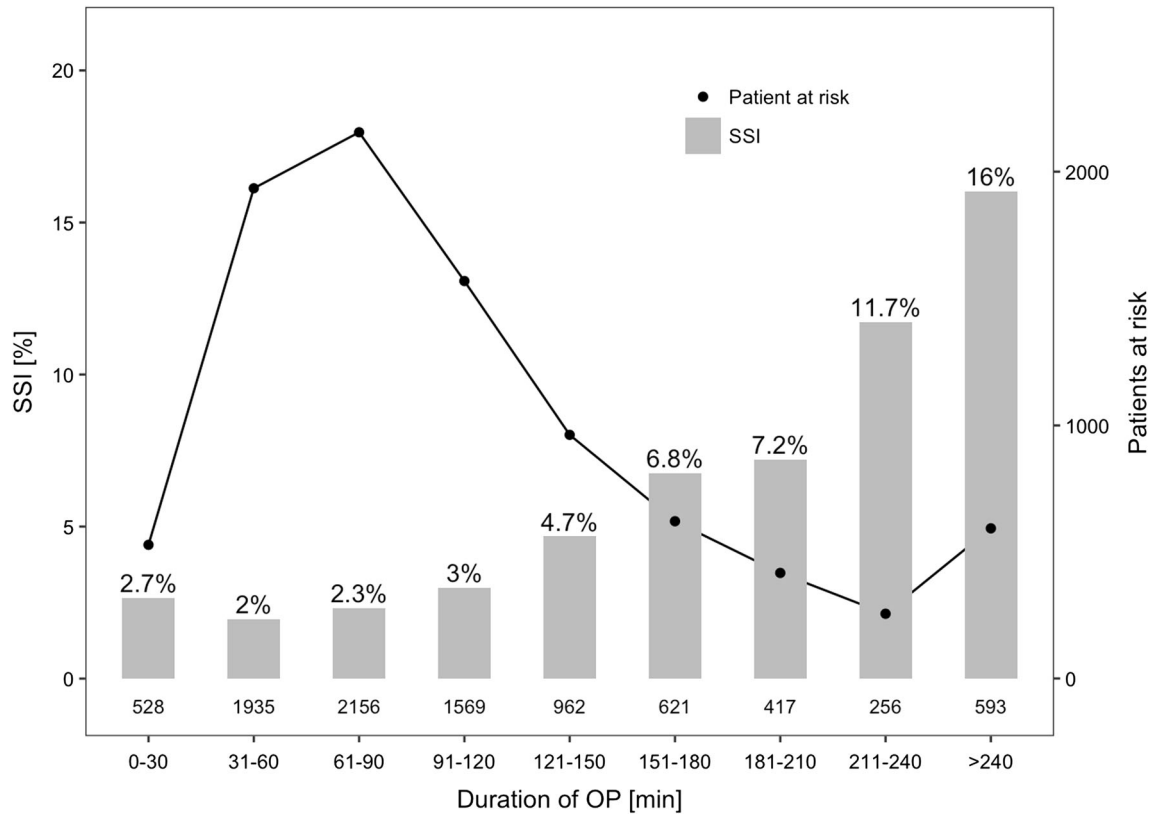

Fig. 1 Long-duration surgical interventions are associated with high incidence of surgical site infections. SSI incidence was evaluated in 9037 patients with class I–III wounds and ASA scores of 1–3 undergoing surgical operations (OP) of the indicated duration. Absolute numbers of patients undergoing OP of defined duration are also shown by the continuous line of "Patients at risk." Dark columns refer to percentages of patients with SSI among those undergoing surgery of the indicated duration

and $n = 283/593$, 47.7%, respectively), whereas 308/593 (52%) had class I wounds (Table 1).

Within this group, SSI incidence was significantly associated with a 48 min longer median duration of operations and an interquartile range about 1.4 times wider, as compared to SSI- cases ($p < 0.001$). Instead, other variables were homogeneously distributed between SSI + and SSI- cases (Table 1). In particular, emergency and elective surgery were characterized by similar SSI incidence ($p = 0.21$), and wound class, ASA score, treatment area, and BMI did not appear to have an impact on it.

Timing of initial amp in patients undergoing prolonged surgery

Timing of initial antibiotic treatment in this group of patients undergoing prolonged surgery was analyzed in detail. First amp dose had to be administered within 1–120 min before skin incision, as previously reported [23, 24]. Indeed, 544/593 patients (91.7%) correctly received it, whereas in 49/593 (8.2%) cases it was not administered at the correct time. However, initial amp timing did not apparently impact SSI incidence since SSI rates did not differ significantly between the two groups ($p = 0.29$).

Redosing timing and full compliance in patients undergoing prolonged duration surgical procedures

Due to their short half-life following initial administration, antibiotics need to be re-administered to patients undergoing long-duration surgical procedures. However, redosing is frequently overlooked or administered with incorrect timing [21, 22]. Indeed, in spite of a duration of intervention exceeding 240 min in all cases, 278/593 (46.88%) patients did not receive any redosing. Furthermore, in 45/307 (7.58%) cases redosing was administered with incorrect timing. Correctly timed redosing was administered to 270/593 (45.53%) patients.

Compliance with the full protocol was then analyzed. Initial amp and correct redosing were administered to 265/593 patients (44.68%), thereby fully complying with clinical recommendations.

Table 1 Descriptive statistics of study population

	Parameters	SSI	no SSI	*p* value
Total: $n = 593$		94 (15.8%)	499 (84.1%)	
Wound class	I	42 (13.6%)	266 (86.4%)	$p = 0.15$
	II	37 (16.8%)	183 (83.2%)	
	III	15 (23%)	50 (77%)	
Treatment area	Visceral	63 (18.6%)	275 (81.4%)	$p = 0.07$
	Traumatology	16 (10.5%)	136 (89.5%)	
	Vascular	15 (14.5%)	88 (85.5%)	
ASA	1	6 (14%)	37 (86%)	$p = 0,77$
	2	40 (15%)	227 (85%)	
	3	48 (17%)	235 (83%)	
Gender	Male	55 (15%)	313 (85%)	$p = 0.43$
	Female	39 (17.3%)	186 (82.7%)	
Hospital entry	Emergency	26 (13.2%)	171 (86.8%)	$p = 0.21$
	Elective	68 (17%)	328 (83%)	
OP duration[†]	Min	345 (279–413)	297 (265–360)	**$p < 0.001$**
Weight[†]	Kg	74 (63–91)	75 (65–86)	$p = 0.50$
Height[†]	cm	171 (165–176)	171 (165–177)	$p = 0.97$
BMI[†]	kg/m^2	25 (22–31)	26 (22–29)	$p = 0.69$
Amp to cut[†]	Min	30 (15–50)	35 (15–55)	$p = 0.29$
Cut to redosing[†]	Min	215 (185–230)	210 (186–230)	$p = 0.32$
Amp to redosing[†]	Min	241 (235–251)	240 (236–250)	$p = 0.70$

In case of nominal variables, numbers and percentages (in parentheses) are provided. Chi-square tests were used to compare distribution of patients with or without SSI. In case of continuous variables, ([†]) median values and interquartile ranges (in parentheses) are also shown. Kruskal–Wallis tests were used to compare medians in patients with or without SSI

Redosing and SSI incidence in patients undergoing prolonged duration surgical procedures

SSI incidence was evaluated in differentially treated patients undergoing long-duration surgical procedures. Univariate analysis did not show significant differences in SSI rates between patients fully complying with the protocol, e.g., receiving correctly timed redosing, as compared to patients incorrectly receiving it ($p = 0.43$).

Patients were then dichotomized based on whether they had received redosing at all, irrespective of timing. In these conditions, a multivariate analysis taking into account wound class, ASA score, and elective versus emergency surgery showed a significantly (95% CI 0.37–0.96, $p = 0.034$) higher SSI incidence in patients who did not receive redosing at all.

Discussion

Perioperative amp plays a major role in the reduction of morbidity and mortality in patients undergoing surgery [2–5]. Long-duration surgical interventions are associated with higher SSI incidence, and adequate amp requires repeated drug administration [15–18]. Redosing significantly impacts on amp effectiveness [21], and failure to administer it results in increased SSI risk and represents a leading cause of noncompliance with amp standards [20, 21]. However, despite specific guidelines, redosing is frequently neglected.

We studied a group of patients undergoing surgery of a duration longer than 240 min, and we evaluated parameters associated with SSI incidence. Our data document that duration of surgery is the only variable significantly associated with higher SSI incidence, whereas wound class, ASA scores, treatment areas, and emergency versus elective hospital entry do not appear to play significant roles. Within this context, the decisive impact of redosing clearly emerges.

Indeed, in spite of a long duration of surgery more than 45% of patients evaluated in our study did not receive any redosing. These data confirm that raising the awareness of the role of correct amp in SSI prevention, e.g., by promoting the participation to dedicated clinical studies, still represents a decisive issue [9–11]. Alternatively, the possibility of using prolonged half-life antibiotics for SSI prevention in long-duration surgery should also be explored.

Multivariate analysis shows that redosing administration significantly reduces SSI incidence. However, our data also indicate that full compliance with amp timing, including redosing time, does not significantly affect its effectiveness. Therefore, more simplified procedures are still effective in SSI prevention during extended duration surgical procedures.

Limitations of our retrospective study should be acknowledged. In particular, the number of variables associated with surgical interventions susceptible of SSI occurrence is extremely high and ranges from operation time, to weight, to associated diseases, fields of intervention, and exact timing of "incorrect" amp redosing. Within this highly heterogeneous context, combinations of variables allowing a reliable multivariate statistical analysis of our data had to be selected, and we chose to emphasize wound class and ASA scores, most frequently referred to as major risk factors for SSI. In this frame, despite the relatively low number of patients receiving it incorrectly ($n = 45$), our data clearly indicate that, irrespective of its timing, redosing represents a critical factor associated with significantly lower SSI rates.

Acknowledgements Support by the Swiss National Science Foundation, the Hospital of Aarau, the University of Basel, the Gottfried und Julia Bangerter-Rhyner Foundation, the Hippocrate Foundation, and the Nora van Meeuwen-Häfliger Foundation is gratefully acknowledged.

Funding This work was partially supported by the Swiss National Science Foundation, the Hospital of Aarau, the University of Basel, the Gottfried und Julia Bangerter-Rhyner Foundation, the Hippocrate Foundation, and the Nora van Meeuwen-Häfliger Foundation.

Compliance with ethical standards

Conflict of interest No conflict of interest to be disclosed.

References

1. Young PY, Khadaroo RG (2014) Surgical site infections. Surg Clin North Am 94:1245–1264
2. Berríos-Torres SI, Umscheid CA, Bratzler DW et al (2017) Centers for disease control and prevention guideline for the prevention of surgical site infection. JAMA Surg 152:784–791
3. Bratzler DW, Dellinger EP, Olsen KM et al (2013) Clinical praxis guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 70:195–283
4. Allegranzi B, Zayed B, Bischoff P et al (2016) New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 16:e288–e303
5. Prospero E, Barbadoro P, Marigliano A et al (2011) Perioperative antibiotic prophylaxis: improved compliance and impact on infection rates. Epidemiol Infect 139:1326–1331
6. Smith BP, Fox N, Fakhro A et al (2012) "SCIP"ping antibiotic prophylaxis guidelines in trauma: the consequences of noncompliance. J Trauma Acute Care Surg 73:452–456
7. Hohmann C, Eickhoff C, Radziwill R et al (2012) Adherence to guidelines for antibiotic prophylaxis in surgery patients in German hospitals: a multicenter evaluation involving pharmacy interns. Infection 40:131–137
8. Putnam LR, Chang CM, Rogers NB et al (2015) Adherence to surgical antibiotic prophylaxis remains a challenge despite multifaceted interventions. Surgery 158:413–419
9. Knox MC, Edye M (2016) Educational antimicrobial stewardship intervention ineffective in changing surgical prophylactic antibiotic prescribing. Surg Infect 17:224–228
10. Murri R, de Belvis AG, Fantoni M et al (2016) Impact of antibiotic stewardship on perioperative antimicrobial prophylaxis. Int J Qual Health Care 28:502–507
11. Levy SM, Phatak UR, Tsao K et al (2013) What is the quality of reporting of studies of interventions to increase compliance with antibiotic prophylaxis? J Am Coll Surg 217:770–779
12. Steinberg JP, Braun BI, Hellinger WC (2009) Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the trial to reduce antimicrobial prophylaxis errors. Ann Surg 250:10–16
13. Ho VP, Barie PS, Stein SL (2011) Antibiotic regimen and the timing of prophylaxis are important for reducing surgical site infection after elective abdominal colorectal surgery. Surg Infect 12:255–260
14. de Jonge SW, Gans SL, Atema JJ et al (2017) Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection: a systematic review and meta-analysis. Medicine (Baltimore) 96:e6903
15. Cheng H, Chen BPH, Soleas IM et al (2017) Prolonged operative duration increases risk of surgical site infections: a systematic review. Surg Infect 18:722–735
16. Scher KS (1997) Studies on the duration of antibiotic administration for surgical prophylaxis. Am Surg 63:59–62
17. Ohge H, Takesue Y, Yokoyama T et al (1999) An additional dose of cefazolin for intraoperative prophylaxis. Surg Today 29:1233–1236
18. Zanetti G, Giardina R, Platt R (2001) Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery. Emerg Infect Dis 7:828–831
19. James M, Martinez EA (2008) Antibiotics and perioperative infections. Best Pract Res Clin Anaesthesiol 22:571–584
20. Miliani K, L'Hériteau F, Astagneau P et al (2009) Non-compliance with recommendations for the practice of antibiotic prophylaxis and risk of surgical site infection: results of a multilevel analysis from the INCISO surveillance network. J Antimicrob Chemother 64:1307–1315
21. Kasatpibal N, Whitney JD, Dellinger EP et al (2017) Failure to redose antibiotic prophylaxis in long surgery increases risk of surgical site infection. Surg Infect 18:474–484
22. Goede WJ, Lovely JK, Thompson RL et al (2013) Assessment of prophylactic antibiotic use in patients with surgical site infections. Hosp Pharm 48:560–567
23. Weber WP, Marti WR, Zwahlen M et al (2008) The timing of surgical antimicrobial prophylaxis. Ann Surg 247:918–926
24. Weber WP, Mujagic E, Zwahlen M et al (2017) Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial. Lancet Infect Dis 17:605–614
25. Rosenthal R, Weber WP, Zwahlen M et al (2009) Impact of surgical training on incidence of surgical site infection. World J Surg 33:1165–1173
26. Weber WP, Zwahlen M, Reck S et al (2009) The association of preoperative anemia and perioperative blood transfusion with the risk of surgical site infection. Transfusion 49:1964–1970
27. Mangram AJ, Horan TC, Pearson ML et al (1999) Centers for Disease control and prevention (CDC) hospital infection control practices advisory committee. Guideline for prevention of surgical site infection. Am J Infection Control 27:97–132

28. Doyle DJ, Garmon EH (2018) American Society of Anesthesiologists Classification (ASA Class). StatPearls Publishing, Treasure Island, FL
29. R Core Team (2018) R Foundation for Statistical Computing. https://www.R-project.org/