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Research Article

**INTRAOPERATIVE REDOSING OF SURGICAL ANTIBIOTIC
PROPHYLAXIS IN ADDITION TO PREOPERATIVE
PROPHYLAXIS VERSUS SINGLE-DOSE PROPHYLAXIS FOR
THE PREVENTION OF SURGICAL SITE INFECTION**¹Dr Muhammad Uzair, ²Dr Muhammad Aarsal, ³Dr Maryam Khan¹PMC no 118656-p, Email: Uxr148@gmail.com, ²PMC no 118651-p,Email: iamavish1000@gmail.com, ³PMC no 118661-p,Email: maryamalikhhan996@gmail.com**Article Received:** September 2022**Accepted:** October 2022**Published:** October 2022**Abstract:**

Objective: The aim of this study was to determine the effect of preoperative surgical antibiotic prophylaxis (SAP) with additional intraoperative redosing compared to single-dose preoperative surgical antibiotic prophylaxis on the incidence of surgical site infections (SSI).

Summary Background Data: Preoperative SAP is standard care for the prevention of SSI. During long surgical procedures, additional intraoperative redosing of SAP is advised, but there is great variability in redosing strategies and compliance rates.

Methods: We performed a systematic search of MEDLINE (PubMed), Embase, CINAHL and CENTRAL on June 25th, 2021 according to PROSPERO registration CRD42021229035. We included studies that compared the effect of preoperative SAP with additional intraoperative redosing to single dose preoperative SAP (no redosing) on SSI incidence in patients undergoing any type of surgery. Two researchers performed data appraisal and extraction of summary data independently. Meta-analyses were stratified per study type.

Results: We included 2 randomized controlled trials (RCT) and 8 cohort studies comprising of 9470 patients. Pooled odds ratios for SSI in patients receiving intraoperative redosing compared to those without redosing were 0.47 (95% CI: 0.19–1.16, I² ¼ 36%) for RCTs and 0.55 (95% CI: 0.38–0.79, I² ¼ 56%) for observational cohorts. There was considerable clinical heterogeneity among antibiotics used and redosing protocols. GRADE-assessment showed overall low certainty of evidence.

Conclusion: Intraoperative redosing of SAP may reduce incidence of SSI compared to a single dose preoperative SAP in any type of surgery, based on studies with considerable heterogeneity of antibiotic regimens and redosing protocols.

Keywords: anesthesia, antibiotics, meta-analysis, prevention, surgery, surgical site infections

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INTRODUCTION:

We used a generic inverse variance random-effects model to estimate a pooled Surgical site infections (SSI) are a common postoperative complication associated with increased hospital stay, morbidity and mortality. [1-4] Surgical antibiotic prophylaxis (SAP) is an effective From the Department of Surgery, Holy Family Hospital, Rawalpindi.

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Data sharing: All data are published in this manuscript, the cited manuscripts or the supplementary appendix. Data can be provided upon request and in agreement of terms. No individual participant' data were used.

Authors' contributions: N.W.: conceptualization, data curation, formal analysis, methodology, software, validation, visualization, writing – original draft; Q. B.: conceptualization, data curation, formal analysis, methodology, validation, writing – original draft; M.dL.: conceptualization, writing – review & editing; M.B.: conceptualization, methodology, supervision, writing – review & editing; S.dJ.: conceptualization, formal analysis, methodology, supervision, writing – review & editing; All authors critically revised the manuscript and approved final manuscript. All authors had full access to all data and responsibility for the decision to submit for publication.

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intervention for the prevention of SSI in indicated procedures. [5] However, administration of antibiotics also has a dose and duration dependent association with adverse effects including the emergence of antibiotic resistance. [6] Therefore, SAP strategies aim to be both optimally effective and restrictive on the amount of antibiotics administered. Administration of SAP before incision is advised but postoperative continuation is discouraged. [7-9]

Evidence of the effect of timely preoperative administration of SAP suggest that adequate tissue concentration is needed at the time of incision and

throughout the procedure for SAP to be effective. [10-12] Similarly, inadequate antibiotic tissue concentration upon wound closure is associated with increased risk of SSI [13] and the redundancy of postoperative continuation of antibiotics depends on timely preoperatively administration and intraoperative redosing. [14] Tissue concentration depends on pharmacokinetics, pharmacodynamics, the initial dose, and the time passed since the initial dose. [15,16] Long procedure duration or excessive blood loss may decrease antibiotic tissue levels, potentially below effective concentrations. [15,16] Intraoperative redosing of SAP increases tissue concentration and has been suggested during longer procedures or after excessive blood loss to help prevent SSI. [5] There is some clinical evidence to support this hypothesis. [17-18]

Recent guidelines have assessed redosing of SAP either as out of scope, [7] deemed too few randomized trials available for proper analysis and recommendation [8] or recommend to give a repeat dose if the surgical procedure is longer than the half-life of the antibiotic. [9] However, the latter recommendation is presented without support of evidence. [9,19] An earlier guideline on SAP by the American Society of Hospital Pharmacists (ASHP) recommended redosing of SAP in long procedures defined as exceeding 2 half-lives of the antimicrobial agent or procedures with excessive blood loss.⁵ Local SAP protocols, such as the American Surgical Care Improvement Program, also advise redosing of SAP in surgical procedures lasting longer than 2 times the half-life of the antibiotic given.^{20,21} Unfortunately, reported compliance is low. [22,23] The conflicting recommendations leave patients and practitioners in uncertainty and inevitably lead to suboptimal care in some cases. To our knowledge no systematic review on the effect of SAP redosing on SSI risk has been performed.

We performed a systematic review and meta-analysis to assess the effect of intraoperative redosing in addition to preoperative SAP compared to a single dose of preoperative SAP on the incidence of SSI. We hypothesized that intraoperative redosing of SAP reduces the risk of SSI.

METHODS:

Search Strategy and Selection Criteria:

We performed a systematic review with meta-analysis according to our pre-registered PROSPERO protocol (CRD42021229035). We report according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [24]

We searched MEDLINE (PubMed), Embase, CINAHL, CENTRAL databases from inception until June 25, 2021. The terms “surgical site infection,” “antibiotic prophylaxis,” “drug administration schedule,” “redosing,” and “perioperative care” were used. A clinical librarian aided the literature search. We performed backward and forward citation tracking to identify additional eligible studies. There were no restrictions on study type, publication date, or language. The search strategy is available in supplementary Appendix 1, <http://links.lww.com/SLA/D732>.

We included randomized controlled trials (RCTs) that compared the effect intraoperative redosing in addition to preoperative SAP (intervention) to a single dose of preoperative SAP (control) on the incidence of SSI in adult patients undergoing elective surgery and observational studies that aimed to estimate the effect [odds ratio (OR) or relative risk (RR)] of additional intraoperative redosing compared to a single dose of preoperative SAP. Intraoperative redosing was defined as the administration of any intraoperative dose of antibiotics after initial preoperative SAP. There were no restrictions on the protocol of redosing concerning timing and dosage. We excluded studies that did not clearly state administration of preoperative SAP or did not clearly distinguish between intraoperative or postoperative redosing or studies that investigated the effects of topical antibiotics. Two authors (N.W. and Q.B.) independently screened all titles and abstracts through Rayyan QCRI.²⁵ Full texts articles of eligible studies were obtained. Articles that fulfilled the inclusion criteria were included. Disagreements were resolved by consensus with a third author. The reference lists of the included articles were cross-checked for additional potential eligible studies.

Outcomes

The primary outcome was (adjusted) OR for SSI after receiving preoperative SAP with additional intraoperative redosing (intervention) compared to a single dose of preoperative SAP (control). Secondary outcomes included SSI related mortality, length of hospital stay, adverse events related to the use of antibiotics such as allergic reactions or *Clostridium difficile* infections.

Data Synthesis

Two authors (N.W. and Q.B.) independently extracted study data following a predefined data extraction form. Data included study type, publication date, country of publication, type of surgery, wound class following the CDC-classification,²⁶ minimum surgery length, antibiotic used, half-life of antibiotic regimen, preoperative SAP, intraoperative redosing strategy,

and its definition in analysis of observational studies, postoperative SAP duration, SSI definition, reported adverse events, number of patients, incidence of SSI, and reported estimated effect. Authors were contacted if insufficient detail of the before mentioned data was reported.

For RCTs, the ORs for SSI were calculated based the SSI incidence in the control and intervention group. For observational studies, we used the reported OR for the participants that received redosing compared to the group that did not receive redosing. To account for confounding in observational studies, we used the reported adjusted. If an adjusted RR was reported and the incidence of the outcome was low (< 10%), we assumed the adjusted RR to be equal to the OR. [27]

Statistical Analysis:

Meta-analyses were stratified per study type. For binary outcomes, we calculated pooled effect estimates as ORs with corresponding 95% confidence intervals (CIs) using a generic invariance random-effects model (DerSimonian and Laird). No continuous outcomes were identified. Heterogeneity was expressed using the I^2 statistic.

The following subgroup analyses were conducted: studies that administered redosing within 2 half-lives after SAP, as this is the most widely recommended regimen [5]; Studies that did continue prophylaxis postoperatively versus studies that did not, as postoperative continuation of SAP might mask a potential benefit of intraoperative redosing. [14] Furthermore, a sensitivity analysis was performed for studies that used a cefazolin-based protocol versus studies that used other agents, as cefazolin is the most widely recommended agent for SAP. [5,28] When at least ten studies per variable were identified, formal meta-regression and subgroup analysis were conducted. Otherwise, exploratory subgroup analysis was performed without meta regression analysis.

Statistical analysis was performed using R version 4.0.3 [R Core Team (2016) R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria R; <https://www.R-project.org/>].

Risk of Bias and Certainty of Evidence:

We used the Cochrane Risk of Bias tool for randomized trials (RoB2) [29] to assess bias in randomized trials and the Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool for cohort studies. [30] A funnel plot was constructed to assess publication bias. [31] If

appropriate, trim-and-fill analysis was performed to analyze the effect on the effect estimate of any potential publication bias. Certainty of evidence was determined following the Grade of Recommendations Assessment, Development and Evaluation (GRADE) method. [32]

RESULTS:

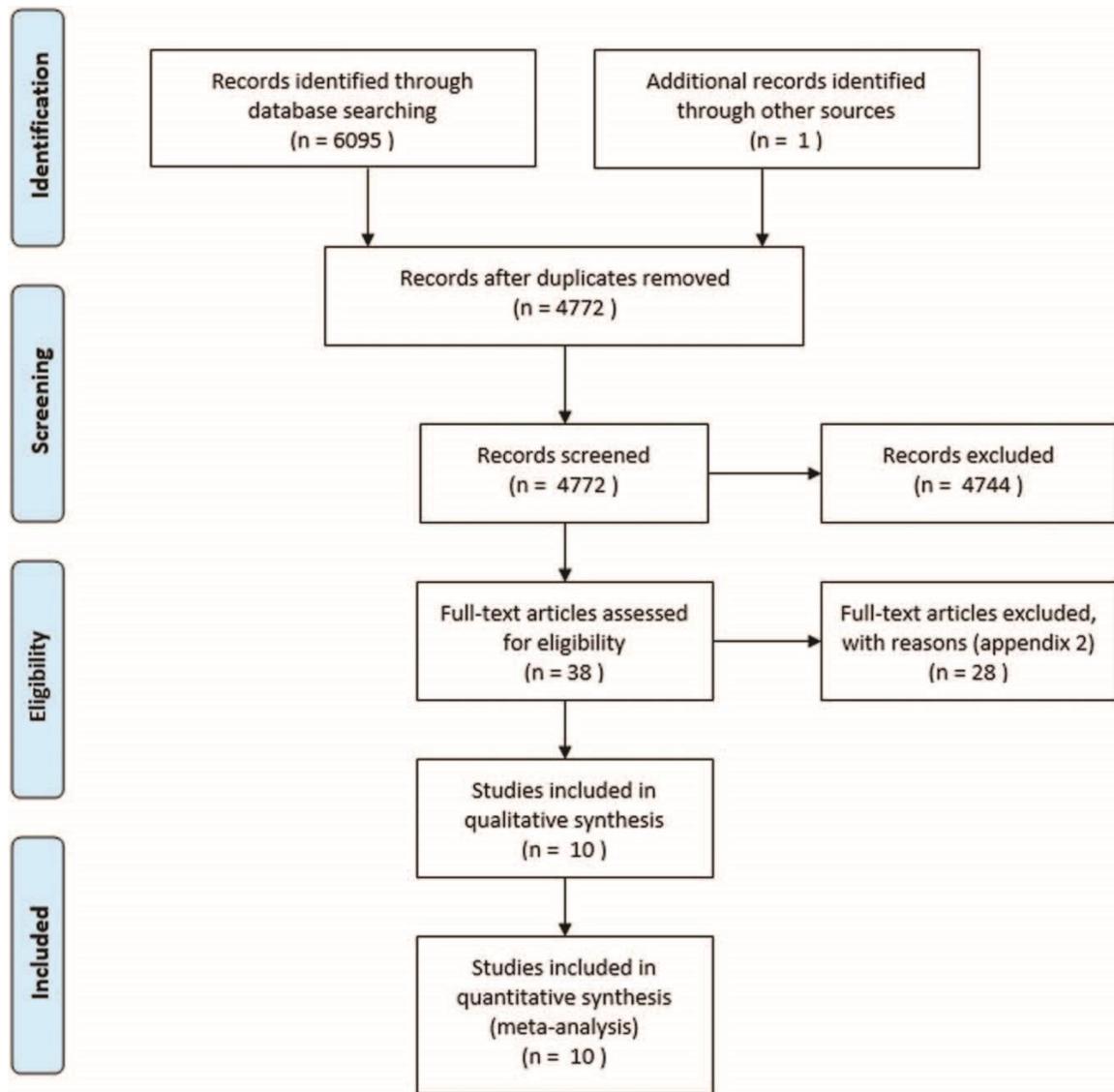
Study Selection:

Figure 1 depicts the article selection process. The search yielded 6095 potential studies. We removed 1324 duplicates. A total of 27 full texts were reviewed. Reasons for exclusion are listed in supplementary Appendix 2, <http://links.lww.com/SLA/D732>. We

included 2 randomized controlled studies [33,34] and 8 observational studies. [17,18,22,23,35–38] One study was retrieved through backward citation tracking. [23] The included studies had 9470 participants and were published between 1997 and 2019.

Study Characteristics:

Study characteristics of the included studies are listed in Table 1. Five studies were conducted in a mixed population of multiple different surgical expertise. [22,23,34,35,37] Most studies were performed with patients undergoing abdominal, [35–37] FIGURE 1. PRISMA flow diagram.



orthopedic/trauma,22,23,34,35 cardiothoracic,18,34,38 gynecologic,22,23,33 or general surgery. [17,23,34]
Redosing Protocols

There was substantial variation in choice of antibiotic regimen and redosing protocols. The majority of the studies included surgical procedures with a minimal duration of 240 minutes.[22,23,35–38] Two studies only used cefazolin,[18,34] 1 study used ampicillin and sulbactam, [33] and the other studies reported several regimens with some including cefazolin. Antibiotic classes and half-lives of the respective antibiotic agents are summarized in Table 2. Preoperative timing varied from within 120 minutes,[23,35] to 90 minutes, [18] 60 minutes, [17,22,36,38] 30 minutes, [34] or 15 minutes [33] preoperatively. Three studies continued prophylaxis postoperatively until up to 48 hours [18,22,36] and 5 other studies reported to have refrained from this. [17,23,33–35] Two studies did not provide sufficient information to assess this; [37,38] we tried contacting those authors, but they did not respond.

Redosing in the 2 RCTs was formalized as intervention at 2 hours after incision [33] and 3 hours after the initial dose. [34] Most observational studies described a local protocol for redosing and differences in compliance permitted analysis of its effectiveness. Absent a formal intervention, adequate redosing was defined in the analysis. This definition varied from any subsequent intraoperative dose after initial preoperative SAP administration [18,35] to strict definitions based on the half-life of the administered agent [17,23] or a set time for any agent. One study also included blood loss exceeding 1500ml in the definition. [23] Like with the RCTs, set point for timing of redosing varied between initial preoperative SAP administration [17,18,23,36,38] or timing of incision. [22,35] One study did not report on the set point for timing of redosing. [37] Six studies reported redosing strategies that resulted in administration within 2 half-lives after initial SAP administration, [17,23,33,34,36,38] 3 did not, [18,22,35] and 1 study provided insufficient information for this assessment. [37]

The number of covariates adjusted for in the analysis of observational studies ranged from 2 [37] to 18. [17] Most studies adjusted for complexity of the procedure (operating time, procedure type, ASA). One study reported 2 models. We used the model based on covariates from baseline characteristics similar to the other studies.

One study compared redosing to no redosing or late redosing. [17] Late redosing constituted 1.46% of the study population.

TABLE 1. Study Characteristics

Author, Year	No. of patients	Type of Surgery	Minimal Length Surgery	Antibiotic Class	Antibiotic Regimen	Redosing Strategy (RCT) or Analysis Definition of Redosing (OBS) & t1/2	SAP Timing (Min. Pre-incision)	Postoperative SAP	Reported Primary Outcome	Covariates Adjusted For
Randomized controlled trials										
Colombo										
	448	Gynecologic surgery	120 min	Penicillin		120min after incision (t1/2: 0.8–1.3)	15	None	C: 32/223 I: 20/225	—
3 et al, 1998	34	Urology, otorhinolaryngology, general, thoracic surgery	180 min	First-generation cephalosporin	Ampicillin (2 g) and sulbactam (1 g) Cefazolin (1g)	180min after initial dose (t1/2: 1.2–2.2)	15–30	None	C: 9/147 I: 2/149	—
Scher, 1997	296	Urology, otorhinolaryngology, general, thoracic surgery	240 min	Cephalosporin, quinolone	Cefuroxime and clindamycin, cefuroxime, cefamandole, other	Redose after 2 times t1/2 or >1.5 L blood loss. (t1/2: 1–2)	< 120 (96%)	None	aOR: 0.60 (0.32–1.12)	Diabetes, use immunosuppressant, wound class, implantations
Prospective observational cohort study	671	General, orthopedic and gynecologic surgery	240 min	Cephalosporin, quinolone	Cefuroxime and clindamycin, cefuroxime, cefamandole, other	Redose after 2 times t1/2 or >1.5 L blood loss. (t1/2: 1–2)	< 120 (96%)	None	Other (4%)	Diabetes, use immunosuppressant, wound class, implantations
Jonge et al, 2021	23	General, orthopedic and gynecologic surgery	240 min	Cephalosporin, macrolide, quinolone, glycopeptide	Cefuroxime and clindamycin, cefuroxime, cefamandole, other	Redose after 2 times t1/2 or >1.5 L blood loss. (t1/2: 1–2)	< 120 (96%)	None	Other (4%)	Diabetes, use immunosuppressant, wound class, implantations
Steinberg 2 et al, 2009	512	Cardiac, orthopedic, gynecologic surgery	240 min	Cephalosporin, macrolide, quinolone, glycopeptide	Cephalosporin, cephalosporin and vancomycin, fluoroquinolones	240min after start but before the end of surgery (t1/2: 1.2–2.2)	< 60	Varying from none up to 48 h	¹⁾ aOR: 0.32 (0.08–1.36) ²⁾ aOR: 1.02 (0.23–4.54)	Hospital, period of measurement, group status, procedure type, procedure duration, ASA score
Retrospective observational cohort	593	Abdominal, vascular and trauma surgery	240 min	Cephalosporin, other	Cefuroxime (1.5 g) with/without metronidazole (0.5 g) ^y	Any intraoperative administration before wound closure	<120	None	aOR: 0.60 (0.37–0.96)	Wound class, ASA, elective vs emergency
Bertschi, 2019	35	Abdominal, vascular and trauma surgery	240 min	Cephalosporin, other	Cefuroxime (1.5 g) with/without metronidazole (0.5 g) ^y	Any intraoperative administration before wound closure	<120	None	aOR: 0.60 (0.37–0.96)	Wound class, ASA, elective vs emergency

(t1/2: 1–2)

Kasatpibal 1 7 et al, 2017	4001	General surgery	n.a.	First- generation cephalosporin, Macrolide, Quinolone	Cefazolin, cefazolin and metronidazole, ciprofloxacin and metronidazole, clindamycin, other	Redose after 1–2 times t1/2 (t1/2: 1.2–2.2)	<60	None	aRR: 0.22 (0.06– 0.75)	Sex, race, in-patient status, origin status, smoking, serum albumin, ASA classification, Emergency surgery, Operative procedure, incision classification, duration of surgery, multiple procedures, antibiotic agent, insulin, crystalloids, colloids, transfusion, blood loss
Morita 3 6 et al, 2005	96	Colorectal surgery	240min After SAP	Cephalosporin	Cephalosporin (1 g)	240min After initial SAP (t1/2: 1.2–2.2)	<60	Yes, unspecified	aOR: 0.09 (0.02– 0.53)	Protocol of administration, DM, procedure, operating time
Zanetti et al, 18 2001	1548	Cardiac surgery	240 min	First- generation cephalosporin	Cefazolin (1 g)	Any intraoperati ve administrati on before wound closure (t1/2: 1.2– 2.2)	< 90	6 additional gifts	¹)aOR: 1.27 (0.80– 2.02) ²)aOR: 0.44 (0.23– 0.85)	Procedure duration, surgeon

37	547	Colorectal or hepatobiliary surgery	240 min First-generation cephalosporin, macrolide, glyco-peptide, other	Cefazolin (2 g) (and metronidazole [0.5 g]), gentamycin (2 mg/kg), and clindamycin (0.6 g), gentamycin (2 mg/kg), and metronidazole (0.5 g)	Every 3 to 12h depending on SAP, based on initial timing of preoperative dose (t1/2: 1.2–2.2)	n.a.	None	aOR: 0.65 (0.35 – 1.22)	Age, operating time
38	1840	Cardiothoracic, orthopedic, vascular, abdominal, and neurosurgery. All patients had diabetes	240 min First-generation cephalosporin	Most commonly; cefazolin	240min After initial dose (t1/2: 1.2–2.2)	< 60	n.a.	aOR: 0.43 (0.24–0.78)	Sex, ASA, operation location, hypertension, blood glucose control, WBC

Agent with shortest t1/2. yBoth antibiotics double dosage if patients weigh >80kg, In cases of known or suspected allergies to these antibiotics, vancomycin (1g), gentamicin (4mg/Kg), and metronidazole or clindamycin (300mg) with or without ciprofloxacin (400mg) were used as alternative treatments.

^zTime between closure and first gift. aOR indicates adjusted odds ratio; aRR, adjusted relative risk; C, control; I, intervention; min, minutes; n.a., not available; t1/2, half-life.

TABLE 2. Half-Life of Antibiotics in Adults With a Normal Renal Function [5]

Antibiotic	Antibiotic Class	Recommended Dose	Half-Life, h
CefazolinAmpicillin β sulbactam	Penicillin	3 g	0.8–1.3
	First-generation cephalosporin	2 g	1.2–2.2
Cefuroxime	Second-generation cephalosporin	1.5 g	1–2
Cefotaxime	Third-generation cephalosporin	1 g	0.9–1.7
Cefoxitin	Second-generation cephalosporin	2 g	0.7–1.1
Clindamycin	Macrolide	900 mg	2–4
Ciprofloxacin	Quinolone	400 mg	3–7
Levofloxacin	Quinolone	500 mg	6–8
Piperacillin-tazobactam	Penicillin	3.375 g	0.7–1.2
Vancomycin	Glycopeptide	15 mg/kg	4–8
Metronidazole	Other	1 g	6–8

Primary and Secondary Outcomes:

All included articles reported a quantitative analysis of the effect of redosing on the incidence of SSI. Several observational studies reported >1 effect estimate because of interaction or subgroup differences. [18,22] All investigated subpopulations met our inclusion criteria and were included in the primary analysis with their combined estimate when available, or as 2 separate estimates when a combined estimate was not reported. No study reported any of the secondary outcomes set for this systematic review.

Meta-Analyses:

Forest plots are presented in Figure 2. Meta-analyses were stratified per study types. Meta-analysis of 2 RCTs resulted in a pooled OR of 0.47 (95% CI: 0.19–1.16, I² ¼ 36%) for SSI for patients that received redosing. Meta-analysis of 8 observational studies resulted in a pooled OR for SSI of 0.55 (95% CI: 0.38–0.79, I² ¼ 56%). Given the similarity in effect estimates, the data were combined and resulted in an OR of 0.54 (95% CI: 0.40–0.74, I² ¼ 50%).

Subgroup and Sensitivity Analyses:

Subgroup of studies that administered redosing within 2 half-lives after initial administration showed a pooled OR for SSI of 0.43 (95% CI: 0.28–0.65, I² ¼ 31%) versus an OR of 0.69 (95% CI: 0.41–1.14, I² ¼ 59%) for studies that reported redosing without this strict interval. Analysis comparing studies that did, and those that did not continue postoperative

prophylaxis resulted in a pooled OR for SSI of 0.58 (95% CI: 0.44–0.77, I² ¼ 0%) for studies that did not continue SAP after surgery, and 0.47 (95% CI: 0.22–1.02, I² ¼ 71%) for studies that did. Pooled OR for SSI for studies that used a cefazolin-based protocol was 0.58 (95% CI: 0.22–1.55, I² ¼ 36%). Plots of additional analyses are shown in the Appendix 4, <http://links.lww.com/SLA/D732> (S1–S5).

Timing of Redosing:

Two studies attempted to investigate the effect of timing of redosing on SSI. One study found no difference between patients that received redosing between 120 and 240 minutes after initial SAP and patients that received redosing either earlier or later than that interval.³⁵ Another study found a significant slope toward less SSI when no redosing, redosing >240 minutes and redosing within 240 minutes were compared,¹⁸ favoring redosing within 240 minutes.

Risk of Bias:

Results of the risk of bias evaluation are presented in Figure 2. The RCTs showed serious risk of bias. Five observational studies were assessed at moderate risk of bias, 1 at serious risk of bias and 2 studies at critical risk of bias. The scores for the individual domains for risk of bias assessment are presented in supplementary Appendix 3, <http://links.lww.com/SLA/D732>.

Too few RCTs were available to plot a funnel plot.

For the observational studies, the funnel plot showed some asymmetry favoring the intervention indicating possible publication bias. Subsequent trim-and-fill analysis imputed 3 studies and resulted in a slightly smaller effect estimate (OR: 0.55 vs OR: 0.65). The funnel and funnel plot after trim-and-fill analysis is presented in the supplementary Appendix 4, <http://links.lww.com/SLA/D732 S6-S7>.

Certainty of Evidence:

The GRADE approach was used for RCTs and cohort studies separately. The summary of findings table is presented in Table 3. There was some risk of bias in the included studies. For RCTs, there was no

inconsistency of results, with low heterogeneity ($I^2 = 36\%$). There was no indirectness of evidence. Publication bias could not be assessed for RCTs. We downgraded the certainty due to imprecision and risk of bias. We assessed the certainty of evidence for RCTs as low. For the cohort studies, we observed serious risk of bias and possible publication bias. We found no indirectness and little inconsistency or imprecision. Residual confounding may cause underestimation of the effect. We deemed certainty of evidence for observational studies very low. Overall, we assessed the certainty of evidence of this systematic review as low.

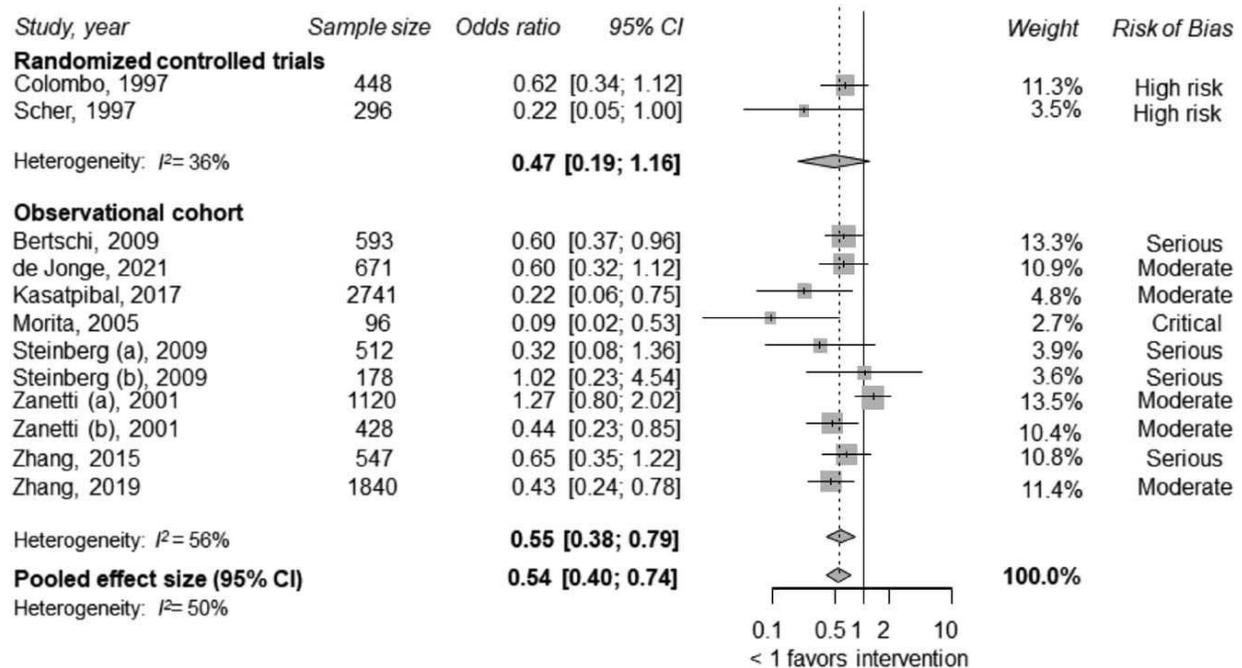


FIGURE 2. Forest plot of meta-analysis. Footprint Figure 2: Two studies reported 2 [A and B] effect estimates because of interaction or subgroup differences.

DISCUSSION:

In this systematic review and meta-analysis, we evaluated the effect of intraoperative redosing in addition to a single dose of preoperative surgical antibiotic prophylaxis (SAP) versus a single dose of preoperative surgical antibiotic prophylaxis on the incidence of SSI. Meta-analysis of 2 RCTs and 8 observational studies resulted in a clear effect in favor of redosing. This effect was most pronounced among studies that administered redosing within 2 half-lives of the administered agent after initial SAP administration and studies that discontinued SAP after surgery. The certainty of evidence was low due to risk of bias and imprecision. Overall, present meta-analysis shows that

intraoperative antibiotic redosing in addition to preoperative SAP may reduce the incidence of SSI compared to a single dose of preoperative prophylaxis.

To our knowledge, this is the first systematic review and meta-analysis on the effect of intraoperative redosing of SAP and the risk of SSI. Current World Health Organization⁷ and Centers for Disease Control and Prevention⁸ guidelines on SSI prevention do not provide a recommendation on intraoperative redosing due to limited clinical evidence. The recent National Institute health and Care Excellence guidelines recommend redosing in surgery taking longer than the half-life of the antibiotic regimen, but this

recommendation is presented without evidence.⁹ An earlier guideline by the ASHP recommended intraoperative redosing after 2 half-lives of the administered agent have passed since initial SAP administration. This recommendation was based on pharmacokinetic principles and evidence that adequate tissue- and plasma concentrations of antibiotics are necessary throughout the surgical procedure to prevent surgical site infection.[11-13] The present systematic review and meta-analysis provides clinical evidence to this context. The effect was more pronounced in studies that provided redosing based on the half-lives of administered agents. Our findings are therefore in line with the existing ASHP recommendation. [5] Although the evidence is formally of low certainty, our findings likely render a sufficiently powered placebo controlled RCT unethical. This leaves little room for further improvement of certainty. Previous research has shown that after adequately timed SAP and intraoperative redosing, postoperative continuation of SAP is obsolete. [14] This aligns with our finding that the effect of redosing is more pronounced in studies that did not continue SAP postoperatively. Future protocols for SAP and quality improvement initiatives should therefore focus on intraoperative redosing after timely preoperative administration.

The exact optimal redosing interval remains unclear and may depend on pharmacokinetic and pharmacodynamics (PK/PD) properties such as the agent, initial dose, blood loss, and protein binding. Further research should focus on optimization of dosing strategies of commonly used agents such as cefazolin and metronidazole) and include PK/PD outcomes such as serum- and tissue levels throughout surgery alongside clinical outcomes. [28] Until then, a pragmatic recommendation such as formulated by the ASHP seems very reasonable. [5]

There are some limitations to consider. The amount of available evidence is limited. We identified only 2 small RCTs that both seem underpowered based on their individual effect estimates. Similarly, there were only 8 observational studies, most of which were small. Observational studies are at risk of confounding due to the lack of randomization of the intervention. Outside of RCTs, redosing typically does not occur at random and reflects long procedure duration, blood loss, or other concerns on infection risk. To account for this, we used adjusted ORs as causal estimates from observational studies. However, residual confounding could still lead to underestimation of the effect. When stratified analysis revealed similar effect estimates of observational studies and RCTs, we combined the 2 in 1 meta-analysis to optimize statistical power with the

limited amount of available data. Although this increased confidence in our effect estimate, the underlying quality and quantity of data remain limited. Subgroup analyses should be considered exploratory and interpreted with caution. Funnel plot and trim-and-fill analysis indicated there was some evidence of publication bias in favor of redosing, suggesting the true effect may be slightly smaller than our estimated effect. Although there was some statistical heterogeneity, almost all variation was in the size and precision of a beneficial effect of redosing. Only 1 observational study indicated potential harm of redosing in shorter procedures but, in the absence of another plausible explanation of redosing of SAP causing infection, this likely represents residual confounding by factors that led the surgeon to administer the second dose.

Although this meta-analysis indicates that intraoperative redosing in addition to preoperative SAP reduces the incidence of SSI when compared to a single dose of preoperative prophylaxis, the certainty of evidence is low. A sufficiently powered placebo controlled RCT examining intraoperative redosing may be unethical given the present findings. The optimal redosing protocol remains unclear and should be the focus of future research.

REFERENCES:

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198–1208.
2. Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet*. 2011;377:228–241.
3. Griskevicius J. European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe 2010-2011. Stockholm: ECDC; 2013.
4. de Lissovoy G, Fraeman K, Hutchins V, et al. Surgical site infection: incidence and impact on hospital utilization and treatment costs. *Am J Infect Control*. 2009;37:387–397.
5. 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.
6. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66:987–994.
7. Global guidelines for the prevention of surgical site

- infection, second edition. Geneva: World Health Organization; 2018.
8. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg.* 2017;152:784–791.
 9. Excellence NifHaC, 2020. Available at: <https://www.nice.org.uk/guidance/ng125>. Accessed July 26, 2020.
 10. de Jonge SW, Gans SL, Atema JJ, et al. Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96:e6903.
 11. Goldmann DA, Hopkins CC, Karchmer AW, et al. Cephalothin prophylaxis in cardiac valve surgery. A prospective, double-blind comparison of two-day and six-day regimens. *J Thorac Cardiovasc Surg.* 1977;73:470–479.
 12. Zelenitsky SA, Calic D, Arora RC, et al. Antimicrobial prophylaxis for patients undergoing cardiac surgery: intraoperative cefazolin concentrations and sternal wound infections. *Antimicrob Agents Chemother.* 2018;62:e0136018.
 13. Zelenitsky SA, Ariano RE, Harding GK, et al. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. *Antimicrob Agents Chemother.* 2002;46:3026–3030.
 14. de Jonge SW, Boldingh QJJ, Solomkin JS, et al. Effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis. *Lancet Infect Dis.* 2020;20:1182–1192.
 15. Ohge H, Takesue Y, Yokoyama T, et al. An additional dose of cefazolin for intraoperative prophylaxis. *Surg Today.* 1999;29:1233–1236.
 16. DiPiro JT, Vallner JJ, Bowden TA Jr, et al. Intraoperative serum and tissue activity of cefazolin and cefoxitin. *Arch Surg.* 1985;120:829–832.
 17. Kasatpibal N, Whitney JD, Dellinger EP, et al. Failure to redose antibiotic prophylaxis in long surgery increases risk of surgical site infection. *Surg Infect (Larchmt)*. 2017;18:474–484.
 18. Zanetti G, Giardina R, Platt R. Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery. *Emerg Infect Dis.* 2001;7:828–831.
 19. Excellence NifHaC. Surgical site infections: prevention and treatment - full guidance. National Institute for Health and Clinical Excellence; 2008.
 20. Bratzler DW, Houck PM, Surgical Infection Prevention Guideline Writers W. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Am J Surg.* 2005;189:395–404.
 21. veiligheidsprogramma V. Praktijkgids ‘Voorkomen van wondinfecties na een operatie’. 2009.
 22. Steinberg JP, Braun BI, Hellinger WC, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Ann Surg.* 2009;250:10–16.
 23. de Jonge SW, Boldingh QJJ, Koch AH, et al. Timing of preoperative antibiotic prophylaxis and surgical site infection: TAPAS, an observational cohort study. *Ann Surg.* 2021;274:e308–e314.
 24. Moher D, Liberati A, Tetzlaff J, et al., Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62:1006–1012.
 25. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5:210.
 26. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol.* 1999;20:250–278. quiz 79-80.
 27. Zhang J, Yu KF. What’s the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280:1690–1691.
 28. The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). 2019.
 29. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:14898.
 30. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.
 31. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629–634.
 32. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64:383–394.
 33. Colombo MZ G, Negri L, Scalabrino S, et al. A randomized comparison of one-dose versus two-dose antibiotic prophylaxis in gynaecologic surgery lasting over two hours. *Italian J Gynaecol Obstet.* 1998;10:9–15.
 34. Scher KS. Studies on the duration of antibiotic administration for surgical prophylaxis. *Am Surg.* 1997;63:59–62.
 35. Bertschi D, Weber WP, Zeindler J, et al. Antimicrobial prophylaxis redosing reduces surgical

- site infection risk in prolonged duration surgery irrespective of its timing. *World J Surg.* 2019;43:2420–2425.
36. Morita S, Nishisho I, Nomura T, et al. The significance of the intraoperative repeated dosing of antimicrobials for preventing surgical wound infection in colorectal surgery. *Surg Today.* 2005;35:732–738.
37. Zhang Y, Mahar AL, Edgar B, et al. Length of surgery and intra-operative best practices determine surgical site infection risk in operations of prolonged surgery. *Can J Infect Control.* 2015;30:158–164.
38. Zhang X, Li T, Li Y, et al. Protective effect of intraoperative re-dose of prophylactic antibiotics on surgical site infection in diabetic patients: a retrospective cohort study. *Ann Transl Med.* 2019;7:96.