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Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection

A systematic review and meta-analysis

Stijn Willem de Jonge, MD[a], Sarah L. Gans, MD, PhD[a], Jasper J. Atema, MD, PhD[a], Joseph S. Solomkin, MD[b], Patchen E. Dellinger, MD[c], Marja A. Boermeester, MD, PhD[a,*]

Abstract

The aim of the study was to assess the effect of timing of preoperative surgical antibiotic prophylaxis (SAP) *on* surgical site infection (SSI) and compare the different timing intervals.

The benefit of routine use of SAP prior to surgery has long been recognized. However, the optimal timing has not been defined. For the purpose of developing recommendations for the World Health Organization guideline for SSI prevention, a systematic review and meta-analysis of all relevant evidence was conducted.

Major medical databases were searched from 1990 to 2016. The primary outcome was SSI after preoperative-SAP comparing different timing intervals. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model.

Fourteen papers with 54,552 patients were included in this review. In a quantitative analysis, there was no significant difference when SAP was administered 120–60 minutes prior to incision compared to administration 60–0 minutes prior to incision. Studies investigating different timing intervals within the last 60 minutes time frame reported contradictive results. The risk of SSI almost doubled when SAP was administered after first incision (OR:1.89; 95%CI:[1.05–3.40]) and was 5 times higher when administered more than 120 minutes prior to incision (OR5.26; 95%CI:[3.29–8.39]).

Administration of antibiotic prophylaxis more than 120 minutes before incision or after incision is associated a higher risk of surgical site infections than administration less than 120 minutes before incision. Within this 120-minute time frame prior to incision, no differential effects could be identified. The broadly accepted recommendation to administer prophylaxis within a 60-minute time frame prior to incision could not be substantiated.

Abbreviations: CABG = Coronary artery bypass graft, CDC = Center for Disease Control and Prevention, CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence interval, CINHAL = Cumulative Index to Nursing and Allied Health Literature, GRADE = Grading of recommendations, assessment and evaluations, MeSH = Medical Subject Headings, OR = odds ratio, RCT = randomized controlled trial, SAP = surgical antibiotic prophylaxis, SSI = surgical site infection, WHO = World Health Organization.

Keywords: antibiotic prophylaxis, guideline, meta analysis, surgery, surgical site infection, systematic review, WHO

1. Introduction

Surgical site infections (SSI) are a dreadful complication in surgery. SSI is one of the most common nosocomial infections accounting for 21.8% of the total in the United States and causes increased morbidity, mortality, readmissions, and prolonged hospital stay.[1,2] As a result, SSI increase healthcare costs up to 1.6 billion dollar a year.[2] Since the introduction of the antisepsis theory by Semmelweis and Lister in the late 18th century, the administration of routine antibiotic prophylaxis in non-clean and implant surgery has been the biggest breakthrough in SSI prevention. The relevance of timing has been proved in experimental and clinical studies.[3,4] However, the optimal timing of administration remains under debate. Classen's landmark study was the first clinical study, describing the least infections when antibiotic prophylaxis was administered within 120 minutes prior to incision. Since then many efforts have been made to define an optimal timing interval within 120 minutes with conflicting results.[5,6] Recently, in a large retrospective cohort, no significant association between timing of AP and SSI was described.[7] Current guidelines issued by professional societies or national authorities, such as the American Society of Health-System Pharmacists,[8] the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America,[9] the Royal College of Physicians of Ireland,[10] or Health Protection Scotland[11] recommend administration within 60 minutes prior to incision. However, these recommendations are not based upon systematic reviews of the literature and

Editor: Duane R. Hospenthal.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands, [b] Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, [c] Department of Surgery, University of Washington Medical Center, Washington, DC.

[*] Correspondence: Marja A. Boermeester, Department of Surgery, Amsterdam, The Netherlands (e-mail: m.a.boermeester@amc.uva.nl).

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Medicine (2017) 96:29(e6903)

Received: 19 December 2016 / Received in final form: 18 April 2017 / Accepted: 19 April 2017

http://dx.doi.org/10.1097/MD.0000000000006903

meta-analysis or a rigorous evaluation of the quality of the available evidence. The contradictive results in previous studies leave the importance of adherence to these guidelines open to discussion. For the purpose of developing recommendations for the new World Health Organization (WHO) SSI prevention guidelines, a systematic literature review and meta-analysis were conducted on the effectiveness of different timing for administration of SAP to reduce SSI in indicated surgical procedures.

2. Methods

The report of this systematic review is drafted in accordance with the MOOSE guidelines for reporting meta analysis of observational studies.[12] As this concerns a literature study, no ethical approval was required. No review protocol for this meta-analysis was published or registered before this study was undertaken. This systematic review is part of the evidence that formed the basis for the recommendations of the WHO guidelines for SSI prevention.

2.1. Search strategy

A clinical librarian was consulted on the search strategy. A systematic search in Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases was conducted. The time limit for the review was between January 1st 1990 and August 13th 2014. The search was updated on August 12th 2016. Language was restricted to English, French, German, and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1, http://links.lww.com/MD/B734).

2.2. Study selection

Two independent reviewers (SW and SG) screened titles and abstracts of retrieved references for potentially relevant studies. Any disagreements were solved through discussion or, when necessary, after consultation of the senior author (MB). The full text of all potentially eligible articles was obtained and reviewed for eligibility based on predefined inclusion criteria. All clinical studies comparing the outcome of surgical site infection with different timing intervals of preoperative antibiotic prophylaxis in indicated procedures were considered for eligibility. This comprised all clean contaminated, contaminated and implant surgery in all surgical fields. Duplicates, congress abstracts, experimental studies, studies with insufficient data for comparison and studies without clear description of the compared timing intervals where excluded from the analysis. This included studies that did not differentiate agents with a prolonged infusion time such as vancomycin or fluroquinolones from fast infusion antibiotics like cephalosporins as timing is generally measured form the moment of administration and a delay to full infusion is anticipated in these drugs. When full text was not available or presented results were incomplete the corresponding author was contacted. When all relevant full text papers were gathered each reference list was reviewed for any omitted studies

2.3. Study quality assessment

Two reviewers (SL, SW), critically appraised each study using the Newcastle–Ottawa Quality Assessment Scale for cohort studies. This is a 8 item scoring system, which is validated in the quality assessment of observational cohort studies in systematic reviews.[13] Any disagreements were resolved through discussion or, when necessary, after consultation of the senior author (MB).

2.4. Data extraction

The 2 reviewers (SL, SW) extracted data in a predefined evidence table. The 2 tables were then compared. Any disagreements were resolved through discussion or after consultation of the senior author (MB). Data collection from each table included; design, scope, number of participants, type of surgery, SSI definition, follow-up duration, antibiotics used, duration of procedure and re-dosing, antibiotic continuation, compared timing intervals, SSI rates, adjusted odds ratios, the variables adjusted for, and quality assessment score.

2.5. Outcome measures

The primary outcome of interest was the incidence of surgical site infection after the administration of antibiotic prophylaxis within different timing intervals from the first incision in non-clean and implant surgical procedures.

2.6. Statistical analysis

All statistical analyses were conducted using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) as appropriate. To account for heterogeneity between studies and confounding variables within studies only adjusted odds ratios where used for the statistical analysis. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison using the generic inverse variance method in a random effects model. When adjusted odds rates were not available unadjusted crude data were used as a surrogate. We assessed statistical heterogeneity with I^2 statistics.

2.7. Publication bias

Publication bias was assessed using a funnel plot.[14]

2.8. GRADE assessment

All data from the eligible studies were analyzed using the grading of recommendations assessment and evaluations methodology (GRADE) with the GRADEpro guideline development tool (http://gdt.guidelinedevelopment.org/), to define the quality of the evidence.[15]

3. Results

3.1. Systematic review

The search retrieved 3177 records of possible relevance. Eleven additional records were identified through other sources. After removal of duplicates 1999 records were screened and 1959 were excluded based on title and abstract. A total of 40 full text articles were assessed for eligibility. Fourteen adhered to the predefined selection criteria and were included in the review; 26 were excluded (Fig. 1, Appendix 2, http://links.lww.com/MD/B734).

3.2. Study characteristics

Characteristics are summarized in Table 1. All studies were observational; no randomized controlled trials (RCT) were

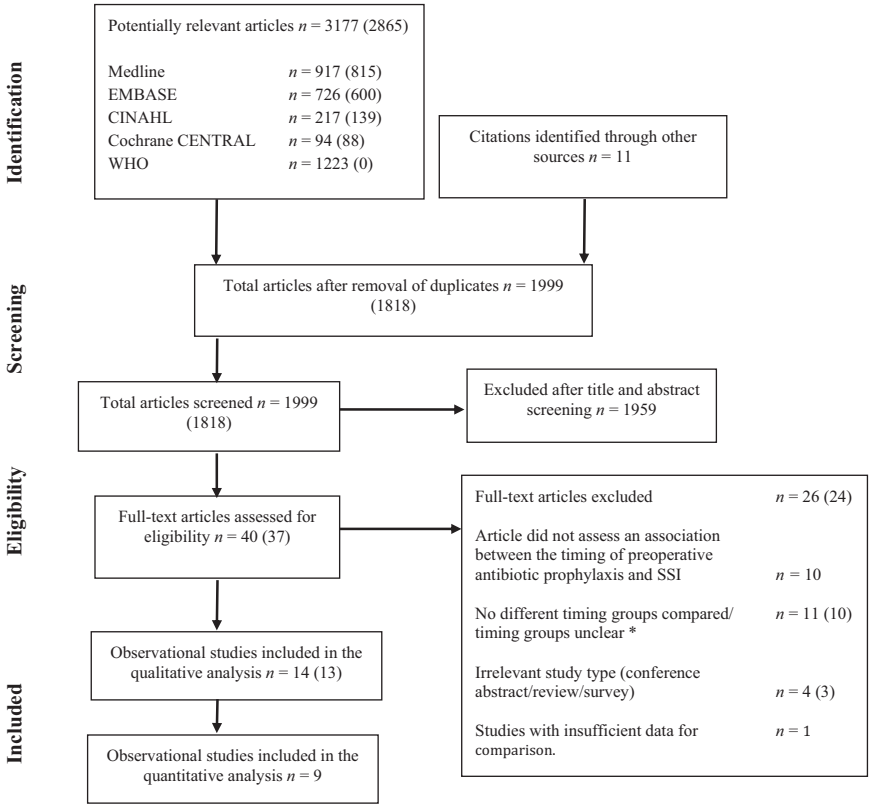

Figure 1. Flowchart of the study selection process. Numbers between parentheses represent the results of the initial search before the update in august 2016 represented by the numbers outside the parentheses. *To avoid drug toxicity, vancomycin and fluoroquinolones have to be infused over a prolonged period of time (>60 min) compared to other antibiotics. As timing is measured from the moment of administration and a delay to full infusion is anticipated with the above-mentioned antibiotics, we considered it necessary to differentiate these from fast infusion antibiotics (for example, cephalosporins). Studies that did not have this differentiation were excluded due to unclear timing categories.

found. Of the observational studies, 1 was a case control study,[16] 2 were retrospective cohorts,[17,18] and 11 were prospective cohorts.[4–6,19–26] Most studies included a variety of surgical procedures. Represented surgical procedures were gastrointestinal, orthopedic, vascular, traumatology gynecology, and cardiac surgery. All but two studies reported the use of the center of disease control and prevention (CDC) or similar standardized criteria for surgical site infection. Only 1 study specified categories of SSI (superficial, deep, organ space) per timing category and reported a similar distribution across timing categories.[5] Four studies considered SSI as an infection occurring before discharge,[4,20,24] 1 before removal of stiches[26] and 9 within 30 days after surgery (or 1 year in the case of implantation of a foreign body).[5,6,16–18,21–23,25] Nine studies reported postoperative antibiotic continuation with a varying duration up to 48 hours.[4–6,17,18,21–23,27] Five studies did not report on postoperative antibiotic regimen.[16,19,20,25,26] Four studies reported a re-dosing regimen within 4 hours after first administration,[6,17,25,26] 3 studies reported a procedure duration not requiring re-dosing,[20,22,23] 7 studies reported no information on re-dosing.[4,5,16,18,19,21,25,28] All but one study used fast infusing antibiotics such as cephalosporin with varying half times.[4–6,16–20,22–26] One study used vancomycine.[21] Ten of the 14 studies reported odds ratios adjusted for confounding variables.[4–6,16,17,19–23] Model building strategies varied and included between 2 and 13 out of 35 individual variables. The variables most frequently adjusted for were procedure duration, age, procedure type, sex, diabetes, and wound classification. The studies described different arbitrary timing intervals varying from 15 to 120 minutes. Despite this heterogeneity in reported time intervals, we were able to make the following comparisons: *post-incision versus pre-incision*,[4,6,17,23] *more than 120 minutes prior to incision versus within 120 minutes*,[4,19,20] *120–60 versus 60–0 minutes*[4–6,21–23] *and 60–30 minutes versus 30–0 minutes prior to incision*[5,6,17,23] (Table 2). 54,552 patients were included in this review of which 21,072 could be included in the meta-analyses. In some cases, participants could be included in several comparisons.

3.3. Critical appraisal

Critical appraisal of the 14 studies showed some differences in methodological quality. All studies were observational and quality was assessed with the Newcastle–Ottawa scale (Table 3). Thirteen were assessed according to the criteria for observational cohort studies.[4–6,17–26] One was assessed according to the criteria for case control study.[16]

Observational cohort studies[4–6,17–26]—approximately half of the cohorts were representative for a variety of surgical specialties.[4–6,19,20,25] The other half included 1 specific specialty or procedure.[17,18,21–24,26] In all the studies, the non-exposed cohort was drawn from the same community as the exposed cohort and ascertainment of exposure was done by review of a secure record like surgical records. All studies demonstrated that the outcome of interest was not present at the start of the study. All but five cohort studies were comparable on the basis of design

Table 1

Study characteristics.

Author, year, reference	Design	N	Population (age, % female,)	Type of surgery	SSI definition, follow-up duration	Antibiotic used	Redosing	Antibiotic continuation	Variables adjusted for	NOS
Classenet al, 1992[4]	Single center OBS-P	2847	53 (11–97); 62%	Hysterectomy, cholecystectomy, bowel resection, gastric bypass, hip, knee.	NA, until discharge	Cefazolin; cefonicid; cefoxitin; cefamandole	NA	24–48 h	Age, procedure type, procedure duration, sex, underlying disease, surgeon, hospital service, attending physician, nursing service, postoperative procedures,	7
Munoz et al, 1995[19]	Single center OBS-P	2083	55.8 ± 20.6; 52%	Clean-contaminated, contaminated and clean.	CDC, until discharge	Cefazolin; clindamycin + gentamicin; gentamicin + metronidazole; ceftriaxone; ceftizoxime; cefotaxime; cefoxitin + gentamicin, cefoxitin.	NA	NA	Procedure duration, diabetes, wound classification	7
Lizan Garcia et al, 1997[20]	Single center OBS-P	1983	48±23; 47%	Clean, clean-contaminated, contaminated, dirty.	CDC, Until discharge	According to the hospital clinical infections commission	NA	NA	Age, procedure duration, wound classification, stay prior to surgery, emergency procedure, ICU stay, malignant neoplasm,	7
Trick et al, 2000[16]	Single center CCTRL	120	NA; NA	CABG	CDC DSSI, 30 d/ 1 y	Cefuroxime	NA	NA	Diabetes, staple use for skin closure, antimicrobial agent	
Garey et al, 2006[21]	Single center OBS-P	2048	64±12; 32%	CABG +valve replacemen. t	CDC, 30 d	Vancomycin	NA	24 hr	Age, procedure type, diabetes, comorbidities, emergency surgery, race, atherosclerosis,	7
Kasatpibal et al, 2006[22]	Multi center OBS-P	1972	26 IQR 16–39; 53.1%	Open uncomplicated appendectomy	CDC, 30 d	Metronidazole + gentamicin	NA	24 hr	Age, procedure type, procedure duration, sex, length of preoperative stay, ASA score,	7
Van Kasteren et al, 2007[23]	Multi center OBS-P	1922	68.8±10.8, 69%	Hip and knee arthroplasty	CDC, 30 d/1 y	Flucloxacillin; erythromycin; clindamycin; cefamandole; amoxicillin; gentamicin	NA	Yes	Age, procedure duration, sex, asa score, duration of prophylaxis, use of antibiotic-impregnated bonce cement	7
Weber et al, 2008[5]	Single center OBS-P	3836	NA; 49%	Visceral, vascular, trauma	CDC, 30 d/1 y	Cefuroxim + metronidazole	NA	Yes	Procedure duration, age, procedure type, sex, diabetes, wound classification, asa score, intraoperative body temperature, body mass index, preoperative antibiotic	8

(*continued*)

Table 1

(continued).

Author, year, reference	Design	N	Population (age, % female,)	Type of surgery	SSI definition, follow-up duration	Antibiotic used	Redosing	Antibiotic continuation	Variables adjusted for	NOS
									therapy, smoking status, immunosuppression,	
Steinberg et al, 2009[6]	Single center OBS-P	3656	NA; NA	Cardiac, hysterectomy, hip and knee, arthroplasty	CDC, 30 d/1 y	Cephalosporin and other short infusion time antibiotics	>4 hr	12–24 hr	Procedure duration, procedure type	8
Ho et al, 2011[17]	Single center OBS-R	605	59.7±17.8; 52%	Colon and rectal surgery with anastomosis	CDC, 30 d	Cefazolin + metronidazol; cefoxitin; fluoro-quinolone + metronidazole	>4 hr	24 hr	Type of surgery, wound class, comorbidities, underlying disease, surgeon, icu admission, intraoperative hypothermia transfusion, history of radiation, serum albumin concentration, intraoperative hypotension, postoperative glycemic control, year	7
Koch et al, 2012[24]	Single center OBS-P	28250	65±12; 28%	Cardiac surgical procedures involving median sternotomy	STS, discharge	Cefuroxime; vancomycin	NA	36 hr	NA	6
El-Mahallawy et al, 2013[26]	Single center OBS-P	200	NA; 31.5%	Cystectomy, gastrostomy, colorectal surgery	CDC, Until removal of stiches	Penicillin +gentamicin; clindamycin + amikacin	>2 hr	NA	NA	5
Koch et al, 2013[25]	Single center OBS-P	4453	54 IQR 42–65; NA	General surgery	NSQIP, 30 d	Cefazolin; ampicillin; ceftizoxime; metronidazole; ciprofloxacin	No	NA	NA	8
Wu et al, 2014[18]	Single center OBS-R	577	NA; NA	Appendectomy	NA, 30 d	Cefazolin; gentamicin; Metronidazole; cefoxitin; cefmetazole	NA	<24 h	NA	6

CCTRL = case-control study; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CABG = coronary artery bypass graft; DSSI = deep sternal site infection; hr = hour; NSQIP = national surgical quality improvement programme; NOS = Newcastle–Ottawa scale, NA = not available; OBS-P = prospective observational cohort; OBS-R = retrospective observational cohort; QR = interquartile range; (): Range; ±: standard deviation; STS = Society of Thoracic Surgeons; SSI = surgical site infection; risk of bias.

Table 2

Results per timing category.

Author, year, reference	Timing categories: Before/after first incision (−/ +)	Timing categories: Time	SSI/total (%)	Adjusted odds ratio (95% confidence interval)	Included in comparison
Classen et al, 1992[4]	−	1440–102 min	14/369 (3.8)	4.3 (1.8–10.4)	1,2,3a
	−	120–0 min	10/1708 (0.6)	1	
	+	0–180 min	4/282 (1.4)	2.1 (0.6–7.4)	
	+	180–1440 min	16/488 (3.3)	5.8 (2.4–13.8)	
Munoz et al, 1995[19]	−	> 120 min	24/107 (22.4)	5.82 (3.12–10.84)	2
	−	< 120 min	28/754 (3.7)	1	
	+	After surgery	94/1222 (7.7)	3.32 (2.04–5.1)	
Lizan Garcia et al, 1997[20]	−	> 120 min	5/8 (62.5)	5.28 (1.56–17.93)	2
	−	< 120 min	249/1975 (12.6)	1	
Trick et al, 2000[16]	−	> 120 min	NA	5 (1.4–17)	NA
	−	< 120 min	NA	1	
Garey et al, 2006[21]	−	> 180 min	21/629 (7.8)	2.1 (0.82–5.62)	3a
	−	121–180 min	48/700 (6.9)	2.6 (1.1–6.2)	
	−	61–120 min	68/888 (7.7)	2.3 (0.98–5.61)	
	−	16–60 min	6/176 (3.4)	1	
	−	0–15 min	4/15 (26.7)	11.6 (2.6–24.7)	
Kasatbipal et al, 2006[22]	−	> 60 min	8/1004 (0.7)	0.22 (0.07–0.70)	3
	−	< 1 60 min	9/814 (1.2)	0.33 (0.11–1.02)	
	+	> 0	4/154 (2.6)	0.78 (0.20–3)	
	NA	None	5/167 (3.0)	1	
Van Kasteren et al,2007[23]	−	> 60 min	5/115 (4.4)	1.3 (0.4–4.4)	1,3a,3b
	−	31–60 min	14/538 (2.6)	0.9 (0.4–2.1)	
	−	1–30 min	25/1143 (2.2)	1	
	+	> 0	6/126 (4.8)	2.8 (0.9–8.6)	
Weber et al, 2008[5]	−	75–120 min	15/201 (7.5)	3.16 (1.4–7.0)	3a,3b
	−	60–74 min	9/263 (3.4)	1	
	−	45–59 min	12/496 (2.4)	1	
	−	30–44 min	33/991 (3.3)	1	
	−	15–29 min	72/1054 (6.8)	2.82 (1.5–5.3)	
	−	0–14 min	39/831 (4.7)	1.75 (0.9–3.4)	
Steinberg et al, 2009[6]	−	> 120 min	4/96 (4.1)	2.11 (0.68–6.59)	1,3a,3b
	−	61–120 min	12/489 (2.5)	1.25 (0.57–2.76)	
	−	31–60 min	38/1558 (2.4)	1.74 (0.98–3.08)	
	−	0–30 min	22/1339 (1.6)	1	
	+	1–30 min	4/100 (4)	1.96 (0.65–5.95)	
	+	> 31 min	5/74 (6.8)	4.18 (1.37–12.75)	
Ho et al, 2011[17]	−	> 30 min	NA	1.725 (1.15–2.6)	1,3b
	−	< 30 min	NA	1	
	+	> 0	NA	0.898 (0.35–2.31)	
Koch et al, 2012[24]	−	75 min	NA (3.7); (4.6*)	NA	NA
	−	60 min	NA (2.8); (3.2*)	NA	
	−	45 min	NA (2.2); (2.2*)	NA	
	−	30 min	NA (1.9); (1.8*)	NA	
	−	15 min	NA (1.8); (2.1*)	NA	
		0 min	NA (2.0); (2.6*)	NA	
	+	15 min	NA (2.4); (3.3*)	NA	
El-Mahallawy et al, 2013[26]	−	> 30 min	12/92 (15)	NA	NA
	−	< 30 min	7/108 (6.9)	NA	
Koch et al, 2013[25]	−	0–30 min	284/3140 (9)	NA	NA
	−	30–60 min	129/1099 (11.7)	NA	
Wu et al, 2014[18]	−	> 120 min	1/15 (7)	NA	NA
	−	12–61 min	15/71 (6.6)	NA	
	−	60–31 min	3/243 (5.3)	NA	
	−	30–0 min	9/249 (3.6)	NA	

-=prior to incision, +=after incision, min=minute, NA=not available, SSI=surgical site infection.

* Second column for vancomycin timing.

and analysis.[4–6,17,19–21,23] One study used no prophylaxis as the reference category.[22] Three studies used a different statistical approach for the analysis.[18,24,25] One study is originally a randomized controlled trial investigating the effect of 2 different agents for antibiotic prophylaxis.[26] The effect of timing was also described, but randomization was done on the basis of the different antibiotic agents and thus we described the study as observational. Assessment of outcome was done by independent

Table 3

Quality assessment, Newcastle–Ottawa scale for nonrandomized studies.

Observational cohort studies, author, year, reference	Representativeness of cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start	Comparability of cohorts	Assessment of outcome	Adequacy of follow-up duration	Adequacy of follow-up of cohorts	Total
Classen et al, 1992[4]	B*	A*	A*	Yes*	*	B*	Discharge	A*	7
Munoz et al, 1995[19]	B*	A*	A*	Yes*	*	A*	Discharge	B*	7
Lizan Garcia et al, 1997[20]	B*	A*	A*	Yes*	*	A*	Discharge	A*	7
Garey et al, 2006[21]	C	A*	A*	Yes*	*	A*	30 days*	A*	7
Kasatpibal et al, 2006[22]	C	A*	A*	Yes*	*	A*	30 days*	B*	7
Van Kasteren et al, 2007[23]	C	A*	A*	Yes*	*	A*	30 days/1 year*	A*	7
Weber et al, 2008[5]	B*	A*	A*	Yes*	*	A*	30 days/1 year*	B*	8
Steinberg et al, 2009[6]	A*	A*	A*	Yes*	*	A*	30 days-1 year*	A*	8
Ho et al, 2011[17]	C	A*	A*	Yes*	*	A*	30 days*	A*	7
Koch et al, 2012[24]	C	A*	A*	Yes*		B*	Discharge	A*	5
El-Mahallawy et al,[26]	C	A*	A*	Yes*	*	D	Until removal of stitches	A*	5
Koch et al, 2013[25]	B*	A*	A*	Yes*		A*	30 days*	B*	7
Wu et al, 2014[18]	C	A*	A*	Yes*		B*	30 days*	A*	6

Case control study Author, year, reference	Is the case definition adequate	Representiveness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment of	Non- response rate	Total
Trick et al, 2000[16]	A*	A*	B	A*	**	A*	Yes*	B	7

Newcastle–Ottawa scale was used. For each * a rating point was added to the total per study.

blind assessment in 10 studies.[5,6,17–23,25] In 2 studies, it was done by record linkage[4,24] and 1 study gave no description of assessment of outcome.[26] Follow-up was 30 days in 8 studies.[5,6,17,18,21–23,25] Four studies considered an SSI as an infection occurring before discharge[4,19,20,24] and 1 until the removal of stiches.[26] All studies were able to complete follow-up of all subjects accounted for or lost very small numbers unlikely to introduce bias.

Case control study[16]—the case definition was adequate. Cases were representative as they consisted of all eligible cases with a surgical site infection over a period of time. Controls were hospital controls from the same population with no occurrence of surgical site infection and results were adjusted for other risk factors. Ascertainment of exposure was done by surgical records in both cases and controls. There are no nonrespondents described.

3.4. Unpooled results

Five studies[16,18,24–26] were not included in any meta-analyzed comparison. Trick et al conducted a case control study in a single center, a different methodology than the other observational studies included in the meta-analysis, and could therefore not be pooled. They included 120 coronary artery bypass graft (CABG) procedures and compared administration more than 120 minutes before incision versus within 120 minutes before incision showing significant increased risk of SSI with administration more than 120 minutes before incision (OR: 5.00; 95%CI: [1.40–17.00]) (Tables 1 and 2, Fig. 2).[16] El Mahallawy et al, Wu et al and 2 studies by Koch et al could not be included in the meta-analysis because adjusted odds ratios could not be derived from their results (Tables 1 and 2, Fig. 2). Koch et al[24,25] conducted 2 observational studies. One prospectively evaluating 28,250 cardiac surgical procedures involving median sternotomy investigated different timings of antibiotic prophylaxis and showed that predicted SSI rates were lowest when cefuroxime was administered 15 minutes prior to incision and vancomycin 30 minutes and the latter evaluated difference between 30 and 60 minutes versus 0 to 30 minutes in 4453 general surgery procedures and showed that administration within 30–60 minutes had a 30% higher risk as compared to administration within 0 to 30 minutes (11.7% vs 9%). This difference was significantly different ($P=.01$). Wu et al compared 577 patients undergoing appendectomy in four 30-minute timing categories ranging from 0 to 30 up to more than 120 minutes prior to surgery and found no significant difference in the SSI rate between the groups. Finally, El Mahallawy et al[26] compared timing of antibiotic prophylaxis more than 30 minutes prior to incision with within 30 minutes in 200 surgical procedures. No significant difference in the SSI rate was found.

In Fig. 2 we have visualized our summary findings.

3.5. Meta-analysis

In 4 separate comparisons, the risk of SSI with different timing intervals could be assessed with meta-analysis. Due to the absence of studies using a 0 to 60 minute interval as reference category we were unable to compare adjusted outcomes for this interval in the analysis. We used unadjusted crude data as a surrogate for this comparison. When crude data was meta-analyzed in the other comparisons it resulted in the same outcome but a smaller effect size as compared to adjusted odds (Appendix 3, http://links.lww.com/MD/B734).

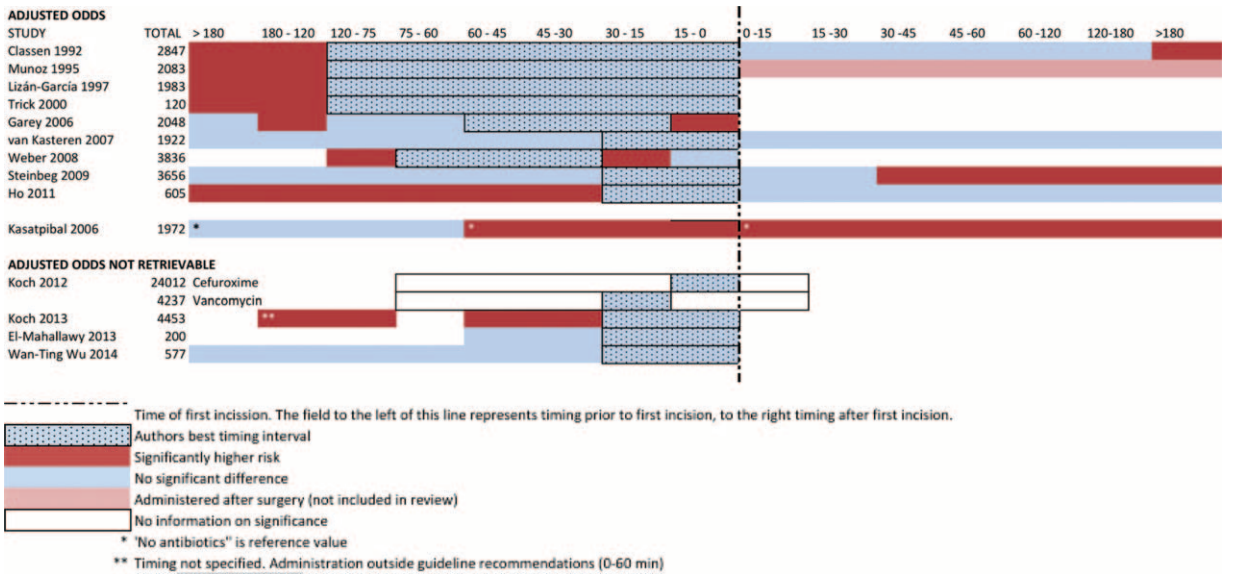

Figure 2. Visualization of results. The table provides a visualization of our findings from all the studies reporting adjusted odds ratios. The vertical dotted line represents the time of first incision. The field to the left of it represents timing prior to first incision, to the right timing after first incision. Blue-bordered fields represent the authors' best timing interval. Blue fields without borders represent timing intervals that do not differ significantly from the reported best interval. Red fields represent intervals with a significant higher risk of SSI.

There was no significant difference in the risk of surgical site infection comparing 120–60 minutes versus 60–0 minutes (OR: 1.22; 95%CI: [0.92–1.61]; Table 2, Fig. 3C). When timing intervals within the last 60 minutes prior to incision, 60–30 minutes versus 30–0 minutes, were compared there was also no significant difference (OR: 1.07; 95%CI: 0.53–2.17; Table 2, Fig. 3D). However, results of individual studies were contradictive and considerable heterogeneity was apparent ($I^2 = 85\%$). When antibiotic prophylaxis was administered after incision the risk of a surgical site infection was almost twice as high (OR: 1.89; 96%CI: [1.05–3.40]; Table 2, Fig. 3A) as compared to administration before incision and resulted in 25 more infections per 1000 treated patients (from 1 more to 65 more). Administration of AP more than 120 minutes prior to incision increased the risk of SSI more than 5 times as compared to administration within 120 minutes (OR: 5.26; 95%CI: 3.29–8.39; Table 2, Fig. 3B).

3.6. Publication bias

Funnel plots are presented in Appendix 4, http://links.lww.com/MD/B734. None of the analyses reached the minimally required 10 included studies for adequate assessment of publication bias. As a result no conclusions can be drawn on the presence or absence of publication bias.

3.7. Grade assessment

GRADE tables with full assessment of the individual comparisons are presented in Table 4. Overall the quality of evidence was very low to moderate due to imprecision, inconsistency and large effect.

4. Discussion

The quality of the retrieved evidence was assessed with the use of GRADE methodology. Overall, moderate to low quality of evidence shows that administration of SAP more than 120 minutes prior to incision, or after incision respectively, is associated with a higher risk of SSI as compared with administration within 120 minutes prior to incision. Within these time limits, no significant difference between timing intervals for SAP administration was demonstrated.

Guidelines and quality control programs have adopted a 60-minute interval for SAP, but the origin of this 60-minute interval is arbitrary. The first published guideline[29] that describes this interval refers to a pharmacokinetic study[30] and a paper investigating the combined results of 2 randomized controlled clinical trials on multidose versus single dose prophylaxis.[31] However, this study was not designed to assess the optimal timing of SAP and very little details about the data and methods are reported. The first clinical study designed to investigate the relevance of timing described the least infections when antibiotic prophylaxis was administered within 120 minutes prior to incision.[4] Regardless of the effect, there was no significant difference with administration 180 minutes after incision.[4] Since then many efforts have been made to define an optimal timing interval within 120 minutes with contradictive results. Some studies suggest that administration of SAP should be within 30 minutes of first incision, whereas other studies have demonstrated an optimal interval between 75 and 30 minutes,[5,6] or describe no relationship at all between timing of SAP and SSI.[7] Although the 60-minute interval is part of daily practice and an important aspect of quality control, not 1 prospective study has confirmed its superiority and a strong evidence based substantiation for its use is lacking.[32,33] In the current systematic review, we aggregate all the available evidence to find an evidence-based answer to the issue of optimal timing of preoperative SAP.

The limitations of the present study are generally allocated to the individual studies. The risk of SSI is a complex and multifactorial problem and therefore prone to confounding. Especially when assessed in observational studies where no randomization is in place to evenly distribute known and unknown confounders across study groups. In this systematic

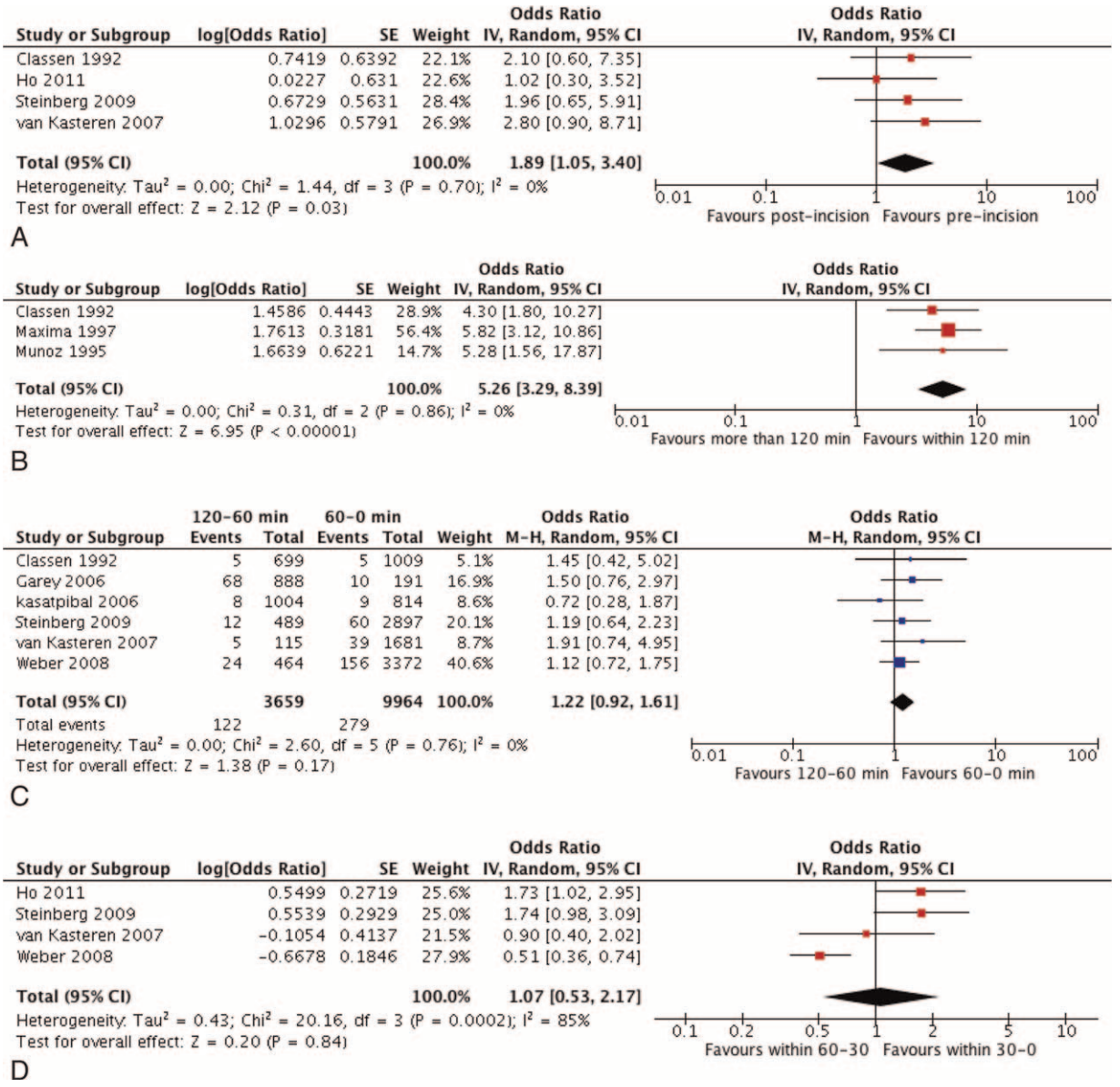

Figure 3. Meta analyses (A) Comparison 1: administration of surgical antibiotic prophylaxis post- versus pre- incision. (B) Comparison 2: Administration of surgical antibiotic prophylaxis more than 120 min prior to incision versus within 120 min prior to incision. (C) Comparison 3a: Administration of surgical antibiotic prophylaxis 120–60 min prior to incsision versus 60–0 min prior to incision. **Crude unadjusted data were used in the meta analyses.* (D) Comparison 3b: Administration of surgical antibiotic prophylaxis 60–30 min prior to incision versus 30–0 min prior to incision.

review and meta-analysis, all identified studies were observational. No randomized studies have been performed on this topic. As a result, design and outcome measures differed limiting inclusion in the meta-analysis, the comparing groups were of unequal size and, while included data are adjusted for measured confounders, model building strategies, and the variables adjusted for varied across studies. Although important variables such as procedure duration, procedure type, and wound classification were included in the majority of the studies, they were not in all. In addition, regardless of the variables included in the models, there is always a risk of unmeasured residual confounding. Therefore inferences on these data are strictly associational, not causal. Also, some of the retrieved evidence is over 20 years old and preferred agents and minimally inhibitory concentrations may have changed. Lastly, among the included studies a substantial heterogeneity was apparent with regard to the antibiotic regimen: all studies used multiple agents with varying half-lives; all studies reported the time of administration, but information on infusion time was lacking in many resulting in the exclusion of all studies that did not differentiate agents with prolonged infusion times such as vancomycin from fast infusing antibiotics such as cephalosporins; the duration of the procedure and re-dosing protocol varied; when a re-dosing protocol was applied, it was based on the duration of the procedure rather than on the time after the first dose, thus leading to a high risk of inadequate re-dosing; and postoperative antibiotic duration was not the same. These are all aspects that potentially influence the effect of timing of SAP on SSI and thereby impede the results. However, despite these limitations, the present systematic review is the first and only to address all the available data on this topic using meta-analysis to aggregate the evidence and GRADE methodology to assess its quality in order to find an evidence-based answer to this issue.

Table 4

Grade table.

Comparison 1: Administration of surgical antibiotic prophylaxis post- vs pre-incision

			Quality assessment				of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With SAP administered after first incision	With SAP administered before first incision	Relative (95% CI)	Absolute (95% CI)	Quality
Surgical site infection											
4	Observational studies	Not serious	not serious	not serious	not serious	none	18/439 (4.1%)	116/3852 (3.0%)	OR: 1.89 (1.05–3.40)	25 more per 1000 (from 1 more to 65 more)	⨁⨁◯◯ Low

Comparison 2: Administration of surgical antibiotic prophylaxis more than 120 minutes prior to incision vs within 120 minutes prior to incision

			Quality assessment				of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With SAP administered within 120 minutes	With SAP administered before 120 minutes	Relative (95% CI)	Absolute (95% CI)	Quality
Surgical site infection											
3	Observational studies	Not serious	Not serious	Not serious	Not serious	Strong association*	287/4437 (6.5%)	43/484 (8.9%)	OR: 5.26 (3.29–8.39)	250 more per 1000 (from 154 more to 361 more)	⨁⨁⨁◯ Moderate

Comparison 3a: Administration of surgical antibiotic prophylaxis 120–60 minutes prior to incision vs 60–0 minutes prior to incision

			Quality assessment				of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With SAP administered 120–60 min	With SAP administered within 60 minutes	Relative (95% CI)	Absolute (95% CI)	Quality
Surgical site infection											
6	Observational studies	Not serious	Not serious	Not serious	Serious†	None	122/3659 (3.3%)	279/9964 (2.8%)	OR: 1.22 (0.92–1.61)	6 more per 1.000 (from 2 fewer to 16 more)	⨁◯◯◯ Very low

Crude unadjusted data were used in the meta-analyses.

Comparison 3b: Administration of surgical antibiotic prophylaxis 60–30 minutes prior to incision vs 30–0 minutes prior to incision

			Quality assessment				of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With SAP administered within 60–30 min	With SAP administered within 30–0 minutes	Relative (95% CI)	Absolute (95% CI)	Quality
Surgical site infection											
4	Observational studies	Not serious	Serious‡	Not serious	Serious§	None	153/3785 (4.0%)	222/4728 (4.7%)	OR: 1.07 (0.53–2.17)	3 more per 1000 (from 22 fewer to 50 more)	⨁◯◯◯ Very low

CI = confidence interval, OR = odds ratio, RR = relative risk, RRR = relative risk reduction, SAP = surgical antibiotic prophylaxis.

* Quality of evidence was upgraded to moderate for large effect size.

† Optimal information size is met but CI overlaps no effect and fails to exclude considerable benefit or harm (RR or RRR of 25%).

‡ High heterogeneity, $I^2 = 85\%$.

§ Optimal information size is met but CI crosses no effect and fails to exclude considerable benefit or harm (RR or RRR of 25%)

Although it has been shown to be very hard to find significant differences between timing categories in individual studies, the pooled analyses of the aggregated show a strong association with harm of inadequate timing.

Our findings indicate that adequate tissue concentrations of the antibiotic should be present at the time of the incision and throughout the procedure for SAP to be effective. This necessitates administration prior to incision. Further evidence shows that low tissue concentration of antibiotics at the time of wound closure is associated with higher SSI rates.[34,35] Although based on the available evidence it is not possible to more precisely establish the optimal timing within the 120-minute interval, antibiotics with short half-lives may be less effective if given early in this time interval than when administered closer to the time of incision, and there is no evidence that administration close to the incision is inferior.[25] It is therefore recommended to take into account the half-life of the administered antibiotics in order to establish the exact time of administration within 120 minutes preincision. (e.g., administration closer to the incision time [<60 minutes] for antibiotics with a short half-life, such as cefazolin, cefoxitin, and penicillins in general) The same attention about the single antibiotic half-life should be paid when considering re-dosing during prolonged surgery, which should occur with the timing based on the time of preoperative administration and not simply on duration of the operation. Concerns about antibiotic protein binding may arise when choosing highly bound antimicrobials, such as ceftriaxone, teicoplanin or ertapenem. Under particular pathophysiological conditions, such drugs disposition may indeed be affected: any situation with low level of serum proteins, such as critically ill or very aged patients, malnourishing, cachexia, or renal diseases with protein loss may yield to suboptimal antibiotic exposure through increased antibiotic clearance in the presence of normal or augmented renal function as well as to overexposure and potential toxic effects in the presence of severely impaired renal function. Difficulties in adherence to recommended timing intervals are seen in various studies.[36–41] The use of SURPASS, a surgical safety checklist, leads to better compliance with regard to timing of antibiotic prophylaxis.[42]

Surgical antibiotic prophylaxis should be administered within 120 minutes prior to incision, when indicated according to the type of operation. Administration before 120 minutes or after incision is associated with a higher risk of surgical site infection. The exact optimal timing within this timeframe cannot be defined according to the available evidence but half-life and protein-binding of the antibiotic should be taken in to account, also according to the underlying conditions of the individual patient. The broadly accepted recommendation to administer AP within 60 minutes prior to incision could not be substantiated. However the evidence comes from studies with limited methodological quality and definitive randomized controlled trials are still needed. Future research should well describe and standardize aspects affecting the effect of timing. Also different pharmacokinetic properties should be taken in account. A protocol for a randomized control trial has been published earlier in 2015.[43] We curiously await the results of this trial. No financial support has been received for this study.

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: 1198–208.

[2] 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;37:387–97.

[3] JF B. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 1961;50:387–97.

[4] Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992;326:281–6.

[5] Weber WP, Marti WR, Zwahlen M, et al. The timing of surgical antimicrobial prophylaxis. Ann Surg 2008;247:918–26.

[6] 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;250:10–6.

[7] Hawn MT, Richman JS, Vick CC, et al. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. JAMA Surg 2013; 148:649–57.

[8] Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect 2013;14:73–156.

[9] Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(suppl 2):S66–88.

[10] Infection JRCoSiIRCoPoIWGoPoSS. Preventing Surgical Site Infections Key Recommendations for Practice. 2012; Available at: https://www.rcpi.ie/wp-content/uploads/2016/01/Preventing-Surgical-Site-Infections-Key-Recommendations-for-Practice.pdf, Accessed 2016.

[11] (SIGN) SIGN. Antibiotic prophylaxis in surgery. 2008 (Updated 2014); Available at: http://www.sign.ac.uk/assets/sign104.pdf, Accessed 2014.

[12] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008–12.

[13] Wells GA, D O'Connell BS, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Toronto: The Ottawa Hospital Research Institute; 2014. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed 2016.

[14] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Research Ed) 1997;315:629–34.

[15] Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

[16] Trick WE, Scheckler WE, Tokars JI, et al. Modifiable risk factors associated with deep sternal site infection after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2000;119:108–14.

[17] Ho VP, Barie PS, Stein SL, et al. Antibiotic regimen and the timing of prophylaxis are important for reducing surgical site infection after elective abdominal colorectal surgery. Surg Infect (Larchmt) 2011;12: 255–60.

[18] Wu W-T, Tai F-C, Wang P-C, et al. Surgical site infection and timing of prophylactic antibiotics for appendectomy. Surg Infect 2014;15:781–5.

[19] Munoz PE, Jimenez Antolin JA, Brea ZS, et al. The effect of surgical antibiotic prophylaxis and the timing of its administration on the risk of surgical wound infection. Rev Clin Esp 1995;195:669–73.

[20] Lizan-Garcia M, Garcia-Caballero J, Asensio-Vegas A. Risk factors for surgical-wound infection in general surgery: a prospective study. Infect Control Hosp Epidemiol 1997;18:310–5.

[21] Garey KW, Dao T, Chen H, et al. Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections. J Antimicrob Chemother 2006;58:645–50.

[22] Kasatpibal N, Norgaard M, Sorensen H, et al. Risk of surgical site infection and efficacy of antibiotic prophylaxis: a cohort study of appendectomy patients in Thailand. BMC Infect Dis 2006;6:111.

[23] van Kasteren ME, Mannien J, Ott A, et al. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 2007; 44:921–7.

[24] Koch CG, Nowicki ER, Rajeswaran J, et al. When the timing is right: antibiotic timing and infection after cardiac surgery. J Thorac Cardiovasc Surg 2012;144:931–7.

[25] Koch CG, Li L, Hixson E, et al. Is it time to refine? An exploration and simulation of optimal antibiotic timing in general surgery. J Am Coll Surg 2013;217:628–35.

[26] El-Mahallawy HA, Hassan SS, Khalifa HI, et al. Comparing a combination of penicillin G and gentamicin to a combination of clindamycin and amikacin as prophylactic antibiotic regimens in

prevention of clean contaminated wound infections in cancer surgery. J Egypt Natl Canc Inst 2013;25:31–5.
[27] Agha A, Alsaudi D, Furnari M, et al. Efficacy of 48-hour post-operative antibiotics prophylaxis for patients undergoing percutaneous endoscopic gastrostomy tube in preventing site infection. J Gastrointestin Liver Dis 2011;20:131–4.
[28] Hollenbeak CS, Murphy DM, Koenig S, et al. The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. Chest 2000;118:397–402.
[29] Dellinger EP, Gross PA, Barrett TL, et al. Quality standard for antimicrobial prophylaxis in surgical procedures. The Infectious Diseases Society of America. Infect Control Hosp Epidemiol 1994;15:182–8.
[30] DiPiro JT, Vallner JJ, Bowden TA, et al. Intraoperative serum and tissue activity of cefazolin and cefoxitin. Arch Surg 1985;120:829–32.
[31] Galandiuk S, Polk HCJr, Jagelman DG, et al. Re-emphasis of priorities in surgical antibiotic prophylaxis. Surg Gynecol Obstet 1989;169:219–22.
[32] Fry DE. Surgical site infections and the surgical care improvement project (SCIP): evolution of national quality measures. Surg Infect (Larchmt) 2008;9:579–84.
[33] Bratzler DW, Houck PM, Writers W, et al. Surgical Infection Prevention GuidelinesAntimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis 2004;38:1706–15.
[34] 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;73:470–9.
[35] Zelenitsky SA, Ariano RE, Harding GKM, et al. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. Antimicrob Agents Chemother 2002;46:3026–30.
[36] White A, Schneider T. Improving compliance with prophylactic antibiotic administration guidelines. AORN J 2007;85:173–80.
[37] Tan JA, Naik VN, Lingard L. Exploring obstacles to proper timing of prophylactic antibiotics for surgical site infections. Qual Saf Health Care 2006;15:32–8.
[38] Rosenberg AD, Wambold D, Kraemer L, et al. Ensuring appropriate timing of antimicrobial prophylaxis. J Bone Joint Surg Am 2008;90: 226–32.
[39] Dellinger EP, Hausmann SM, Bratzler DW, et al. Hospitals collaborate to decrease surgical site infections. Am J Surg 2005;190: 9–15.
[40] Castella A, Charrier L, Di LV, et al. Surgical site infection surveillance: analysis of adherence to recommendations for routine infection control practices. Infect Control Hosp Epidemiol 2006;27:835–40.
[41] Bull AL, Russo PL, Friedman ND, et al. Compliance with surgical antibiotic prophylaxis–reporting from a statewide surveillance programme in Victoria, Australia. J Hosp Infect 2006;63:140–7.
[42] de Vries EN, Dijkstra L, Smorenburg SM, et al. The SURgical PAtient Safety System (SURPASS) checklist optimizes timing of antibiotic prophylaxis. Patient Saf Surg 2010;4:6.
[43] Mujagic E, Zwimpfer T, Marti WR, et al. Evaluating the optimal timing of surgical antimicrobial prophylaxis: study protocol for a randomized controlled trial. Trials 2014;15:188.