Specific Care Question

In children undergoing cardiac, orthopedic, or neuro-shunt surgery, is there harm in completing vancomycin versus not completing vancomycin infusion prior to first incision? Harms include surgical site infections (SSI), mortality, length of stay or costs.

Recommendations Based on Current Literature (Best Evidence) Only

A strong recommendation is made for starting vancomycin within 120 minutes of first surgical incision and completing the infusion prior to the first incision. The overall certainty in the evidence is low[a]. See Table 1. Harms of SSI, hospital length of stay, and cost were all lower in patients who met optimal timing of preoperative antibiotics. Harms that may be important to a pediatric population such as fear, pain, need for distraction, extravasation, traumatic intravenous catheter placement, or loss of intravenous access (Elsevier Clinical Skills, 2020) were not measured as outcomes in any included study.

*Three national guidelines/societies (Berrios Torres et al., 2017; Bratzler et al., 2013; Rangel et al.) agree that preoperative antibiotics should be infused to assure a bactericidal concentration of the medication is established prior to first incision. Most antibiotics can be infused over 15 -30 minutes (Bratzler et al. 2013). However, vancomycin requires a long infusion time to prevent an idiopathic hypersensitivity reaction called vancomycin flushing reaction (*Austin, Foster, & Empey, 2020; *Polk, 1988). It is recommended that preoperative vancomycin infusions start within 120 minutes of infusion to prevent the hypersensitivity reaction, and at least one cohort study shows patients who had vancomycin infusion that started 0 to 15 minutes prior to first incision had increased number of SSI compared to those who had infusion 15-120 minutes prior to first incision.*

The overall certainty of the evidence is low[a]. The included studies were all cohort studies, not randomized trials. The studies were not the same surgery type and the definition of optimal timing of vancomycin infusion varied among studies, see Table 3. However, a large effect size was found in the reduction of SSI when vancomycin was administered within the optimal time frame (see Table 1). Three national guidelines/societies concur on the importance of obtaining proper concentration of vancomycin and avoiding the known effect of too rapid infusion of vancomycin. If vancomycin were infused within the optimal time frame, there would be 54 fewer SSI per 1,000 patients undergoing cardiac or orthopedic surgery, with a range of 53 to 71 fewer infections (see Table 1).

Literature Summary

Background. The Centers for Disease Control and Prevention (CDC) Guideline for Prevention of Surgical Site Infection, the American Pediatric Surgical Association Outcomes and Clinical Trials Committee, and American Society of Health System Pharmacists (ASHP) make congruent recommendations to administer preoperative antimicrobial medications timed such that bactericidal concentration of the agents is established when the incision is made (Berrios-Torres et al., 2017; Bratzler et al., 2013; Rangel et al., 2015). The CDC guideline is unable to refine the recommendation on timing of medication due to lack of randomized control trials that evaluated prophylaxis and the risk of SSI (Berrios-Torres et al., 2017). The inability to make a strong recommendation on timing is echoed by Rangel et al. (2015), who stated heterogeneity of studies on the timing of preoperative antibiotics decreases their certainty in making a strong recommendation regarding the question of preoperative antibiotic timing. However, Rangel et al. (2015) endorses the guidelines by the CDS and ASHP.

The Surgical Care Improvement Project (SCIP) developed quality initiatives to standardized infection prevention measures for adult surgeries and was introduced by the Centers for Medicare & Medicaid and the CDC) in 2006 (Centers for Medicare & Medicaid and the Joint Commission, 2020; Rosenberger, Politano, & Sawyer, 2011). Germane to the question of this CAT, SCIP recommends that prophylactic antibiotics should be infused within one hour prior to surgical incision (Rosenberger et al., 2011). There is an exception for a subset of medications: vancomycin and fluoroquinolones. These subsets require longer infusion times ranging from within 60-120 minutes prior to incision due to idiopathic hypersensitivity reactions (Solensky, 2020; Weller, 2020). For vancomycin, a rate dependent hypersensitivity reaction is called “vancomycin flushing reaction” Austin, Foster, & Empey, 2020 . It is characterized by histamine release and causes flushing primarily in the head and neck region. It is prevented by slowing the rate of vancomycin infusion (Khan & Solensky, 2010; Weller, 2020). The recommended rate of infusion of vancomycin infusion is no faster than 10 mg/minute for a one-gram dose, or over a minimum of 100 minutes, whichever is slower to prevent vancomycin flushing reaction (Polk, 1988; Austin, Foster, & Empey, 2020).

Vancomycin is used as part of alternative antibiotics for children with allergy to *B*-lactam agents, or children colonized with methicillin resistant staphylococcus aureus [MRSA] (Bratzler et al., 2005). The prolonged time to administer vancomycin is a barrier to completing the infusion prior to incision in children. The Surgical Site Infection Improvement Team desires to understand potential harms of incomplete infusion of vancomycin at first incision. This review will summarize identified literature to summarize current literature on the topic.

Study characteristics. The search for suitable studies was completed on June 1, 2020. N. Price MD and K. Fehlhafer, RN, BSN, MBA, CNOR reviewed the 30 titles and/or abstracts found in the search and identified[b] two guidelines and 13 single studies believed to answer the question. After an in-depth review of the guidelines[c] (Berrios-Torres et al., 2017; Bratzler et al., 2013) and six single studies[d] (Burger, Hansen, Leary, Aggarwal, & Keeney, 2018; Cotogni et al., 2017; Crews et al., 2018; Garey et al., 2008; Garey et al., 2006; Malhotra et al., 2020) answered the question specific to the timing of preoperative infusion of vancomycin. (see Figure 1[e]).

Two guidelines and six individual studies were reviewed. The CDC Guideline (Berrios-Torres et al., 2017) and the ASHP Guideline (Bratzler et al., 2013) each provides guidance on many topics including preoperative-dose timing. See Table 2 for AGREE II[c] scores. Crews et al. (2018) evaluated a cohort of 22 pediatric patients who underwent vertical expandable prosthetic titanium rib surgery (VEPTR) to identify risk factors for SSI. Burger et al. (2018) was a retrospective study in adults evaluating whether a first-generation cephalosporin delivered alone or in combination with vancomycin, or if timing of vancomycin administration given in combination, or if vancomycin given in a single dose had an effect on prosthetic joint infection after total hip or knee arthroplasty. Three studies reported upon the timing of preoperative vancomycin in cardiothoracic surgery (Cotogni et al., 2017; Garey et al., 2006). Malhotra et al. (2020) is a report of an adult quality study reports SSI rate if vancomycin infusion start time met SCIP standards or not. Harms specific to pediatric populations such as, fear, pain, need for distraction, traumatic intravenous catheter placement extravasation, or loss of intravenous access (Elsevier Clinical Skills, 2020) are not included as outcomes in any included study.

Summary by Outcome

SSI. Four studies (Burger et al., 2018; Cotogni et al., 2017; Crews et al., 2018; Garey et al., 2006) measured number SSI, (*N* = 3830). *OR* indicated results as counts of infection and they are included in the meta-analysis (see Figure 2 & Table 1). The *OR* = .24, $p < .01$, 95% CI [.13, .44] indicated the intervention of optimal timing of vancomycin administration was favorable to prevention SSI. When vancomycin infusions were initiated within an optimal timeframe there were 54 fewer SSIs, range 53 fewer to 71 fewer SSI.

Malhorta et al. (2020) is not included in the meta-analysis since decreasing SSI was not a goal of the report. However, it is reported that SSI could be predicted based on vancomycin infusion timing. If vancomycin was infused between 60 and 120 minutes prior to incision, the odds of an SSI were not different, *OR* = 1.4, $p = .027$, 95% CI [0.75, 2.73]. However, if vancomycin infusion start time was less than 15 minutes prior to the surgical incision, if the vancomycin infusion start time was less than 15 minutes prior to the surgical incision the odds of a surgical infection were significantly greater., *OR* = 4.23, $p < .001$, 95% CI [2.32, 7.74], and if start time was no later than 25 minutes prior to incision, the odds of an SSI were also significantly greater, *OR* = 3.16, $p < .001$, 95% CI [1.77, 5.66].

Certainty of the evidence for SSI. The certainty of the body of evidence was low ba

sed on four factors[a]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Cohort studies start as having low certainty in the results[a]. The body of evidence was assessed as having very serious inconsistency, or heterogeneity. Definitions of optimal timing of antibiotic infusion varied, as did the length of follow up time, see Table 3. Four studies are in adults (Burger et al., 2018; Cotogni et al., 2017; Garey et al., 2008; Garey et al., 2006) while only one (Crews et al., 2018) was a pediatric study. Three studies included cardiovascular surgeries (Cotogni et al., 2017; Garey et al., 2008; Garey et al., 2006), one study was in joint replacement surgeries (Burger et al., 2018) and one study was for VEPTR (Crews et al., 2018). Although three of the four studies had adult subjects, the studies were not downgraded for indirectness. Bratzler et al. (2013) states the ASHP guidelines are the same for pediatrics and adults with respect to timing of administration. Due to the large effect size, the certainty of evidence was upgraded from very low to low certainty[a].

Upgrading observational studies is rare. To confirm the appropriateness of upgrading, sensitivity analyses was performed. When only studies that describe optimal timing as within 60 minutes of incision, the odds of SSI where vancomycin was infused within the optimal time were significantly less *OR* = .39, *p* < .008, 95% CI [.20, .78] (Crews et al., 2018; Garey et al., 2006). When only adult cardiac surgeries were analyzed, odds of SSI where vancomycin was infused within the optimal time were significantly less, *OR* = 0.26, *p* = .004, 95% CI [.10, .66] (Cotogni et al., 2017; Garey et al., 2006). Upgrading to low certainty of the evidence was agreed upon by the expert opinion from the Department of EBP. Malhorta et al. (2020) which is not included in the meta-analysis, is a well-done cohort study that concurs with the meta-analysis. It reported if any antibiotic was infused < 25 minutes prior to incision for the outcome predicted SSI, *OR* = 3.2, 95% CI [1.76. 5.66].

Table 3
Sources of Heterogeneity in the Studies Included in the Meta-analysis

Study Name	Population	Intervention		Follow-up time
		Optimal timing	Without optimal timing	
Burger et al. (2018)	Adult joint replacement	Started at least 45 minutes prior to incision	Started less than 45 minutes prior to incision	1 year
Cotogni et al. (2018)	Adult cardiac surgery	Incision after completion of vancomycin infusion	Incision prior to completion of vancomycin infusion	30 days
Crews et al. (2018)	Pediatric rib expansion surgery	Strict interval – antibiotic 1 to 30 minutes prior to incision except vancomycin administered within 60 minutes	Standard interval – antibiotic 1 to 60 minutes prior to incision, except vancomycin administered within 120 minutes	6 months
Garey et al. (2006)	Adult cardiac surgery	16 to 60 minutes prior to incision	0-15 minutes or 61 to > 180 minutes prior to incision	30 days

Mortality. One study (Cotogni et al., 2017) measured mortality, (*n* = 741). For the comparison, vancomycin infusion completed prior to incision versus not complete prior to incision, mortality was lower in the group with complete vancomycin infusion before incision, *OR* = .28, *p* < .001, 95% CI [0.14, 0.56].

Certainty of the evidence for Mortality. The certainty of the body of evidence was very low based on four factors[a]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Cohort studies start as low certainty. The body of evidence was assessed to have serious imprecision. The low number of events (*n =40)* decreases certainty in the finding. Sensitivity analysis was not performed. The presence of diagnoses such as diabetes mellitus or lung disease may have confounded the findings. As only one study (Cotogni et al., 2017) was identified to answer this question consistency could not be assessed.

Length of stay. One study reported on hospital length of stay (Garey et al., 2008). Patients who received vancomycin with appropriate timing (*n* = 928) had median (IQR) hospital length of stay of 9 (7-14) days, while patients who received vancomycin with inappropriate timing (*n* = 738) had median (IQR) hospital length of stay of 10 (8-17) days, which is significantly different, *p* < .001..

Certainty of the evidence for length of stay. The certainty of the evidence was very low based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*[a]. Cohort studies start as low certainty. For this outcome the evidence was assessed to have very serious indirectness as chronic diagnoses such as diabetes mellitus or chronic obstructive pulmonary disease may have greater prevalence in adult populations and influence length of stay. As only one study (Garey et al., 2008) was identified to answer this question inconsistency could not be assessed, and there is insufficient evidence to draw a conclusion.

Cost. Two studies reported on cost (Garey et al., 2008; Malhotra et al., 2020). Patients who received vancomycin with appropriate timing (*n* = 928) had median (IQR) costs of $25,321 ($19,429 – $35,471) USD, while patients who received vancomycin with inappropriate timing (*n* = 738) had median

(IQR) cost of $29,475 ($21,507 - $46,488) USD (Garey et al.2008). Similarly, a subgroup analysis (*n* = 88) performed by Malhorta et al. (2020) reported a 208% increase in cost for patients who had vancomycin specifically too close to incision time versus those who had standard infusion times. For this group of patients, total cost of care was 3.47 million USD/year higher in those who received vancomycin too close to incision time.

Certainty of the evidence for cost. The certainty of the evidence was very low based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*[a]. Cohort studies start as low certainty. For this outcome, the evidence was assessed to have very serious indirectness as chronic diagnoses such as diabetes mellitus or chronic obstructive pulmonary disease may have greater prevalence in adult populations and influence the outcome Cost. As two divergent studies were identified to answer there is insufficient evidence to draw a conclusion (Garey et al., 2008; Malhotra et al., 2020).

Identification of Studies

Search Strategy and Results (see Figure 1[e])

PubMed

(vancomycin) AND ("Time Factors"[Mesh] OR timing OR "time to incision") AND ("Surgical Wound Infection"[Mesh] OR "surgical site infection" OR pre-operative OR preoperative OR ("Antibiotic Prophylaxis"[Majr] AND (surgical OR surgery OR pre-operative OR preoperative)))

Records identified through database searching *n* = 27

Additional records identified through other sources *n* = 3

Studies Included in this Review

Citation	Study Type
Berrios-Torres et al. (2017)	CDC Guideline
Bratzler et al. (2013)	ASHP Guideline
Burger et al. (2018)	Retrospective cohort
Cotogni et al. (2017)	Prospective cohort
Crews et al. (2018)	Nested case-control
Garey et al. (2006)	Prospective cohort
Garey et al. (2008)	Prospective cohort
Malhotra et al. (2020)	Retrospective cohort

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Authors	
Classen et al. (1992)	Does not include vancomycin
de Jonge et al. (2017)	Only one study in this systematic review included vancomycin, it is an included study (Garey et al., 2006)
Hawn et al. (2006)	Does not address occurrence of SSI
Hawn et al. (2013)	Does not address optimal vs. non-optimal timing
Hicks and Hernandez (2011)	Narrative review
Koch et al. (2013)	Excluded vancomycin administration
Poe-Kochert et al. (2020)	Abstract only

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings table for this analysis.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]The Appraisal of Guidelines Research and Evaluation II (AGREE II) is an international instrument used to assess the quality and reporting of clinical practice guidelines for this analysis (Brouwers et al. 2010).

[d]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[e]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Brouwers, M.C. et al. for the AGREE Next Steps Consortium. (2010) AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Canadian Medical Association Journal, 182*, E839-842. Retrieved from https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf

[d]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[e]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
ASHP	American Society of Hospital System Pharmacists
CABG	Cardiac Artery Bypass Graft
CAT	Critically Appraised Topic
CDC	Centers for Disease Control and Prevention
EBP	Evidence Based Practice
MRSA	Methicillin Resistant Staphylococcus Aureus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SCIP	Surgical Care Improvement Project
SSI	Surgical Site Infection

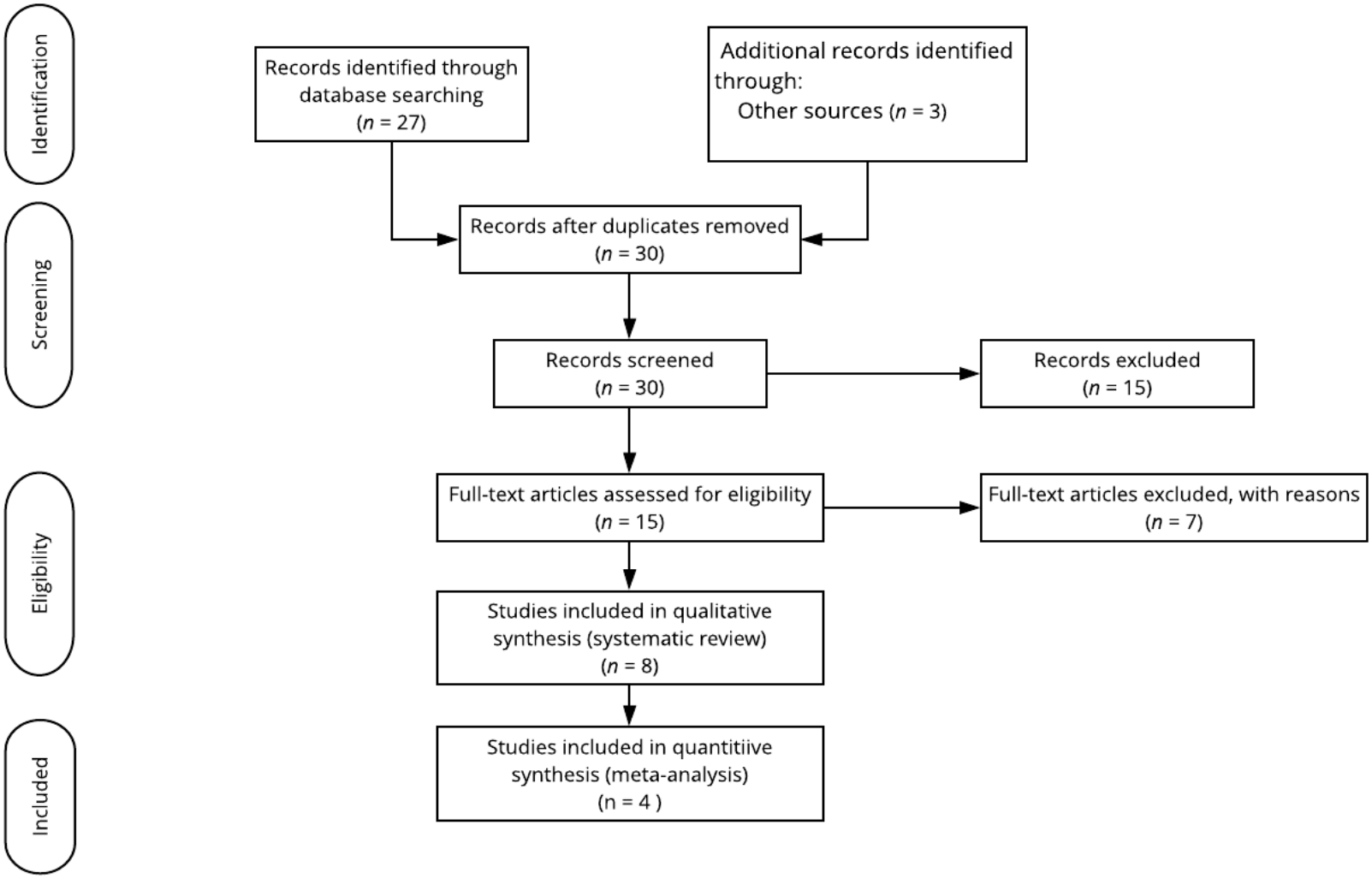


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]

Table 2

AGREE II[c] Summary for the CDC Guideline (Berrios-Torres et al., 2017) and the ASHP Guideline

Domain	Percent Agreement	Percent Agreement
	Berrios-Torres et al. (2017)	Bratzler et al. (2013)
Scope and purpose	100%	100%
Stakeholder involvement	62%	66%
Rigor of development	88%	83%
Clarity and presentation	86%	100%
Applicability	79%	35%
Editorial independence	100%	100%
Overall guideline assessment	100%	100%
Team's recommendation for guideline use	Yes	Yes

Note: One EBP Team members or Scholars completed the AGREE II on the guidelines.

Table 1

Summary of Findings Table: Timing of Vancomycin Infusion

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Without optimal timing	With optimal timing	Relative effect (95% CI)	Risk with without optimal timing all studies	Risk difference with
SSI											
3830 (4 studies) observational	not serious	serious[a]	not serious[b]	not serious	Publication bias undetected strong association	LOW	207/2676 (11.0%)	27/1154 (1.4%)	**OR 0.24** (0.13 to 0.44)	77 per 1,000	**54 fewer per 1,000** (from 71 fewer to 53 fewer)

Notes: [a]The I^2 *statistic* = 34%, which is good. Desired is < 50%. Lower is better, however, various definitions for "optimal timing" were used, and the surgeries were cardiac, and adult or pediatric orthopedic procedures. See Table 3. [b]Although 3/4 studies are in adults, the ASHP states recommendations for perioperative antibiotic administration is the same for pediatrics as adults, except for dosing (Bratzler et al., 2013). It is noted that pediatric recommendations are derived from adult studies.

Meta-analysis

Study or Subgroup	With optimal timing Events	Total	Without optimal timing Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Burger 2018	1	476	13	477	8.1%	0.08 [0.01, 0.58]
Cotogni 2017	13	436	47	305	41.5%	0.17 [0.09, 0.32]
Crews 2018	7	66	6	22	18.9%	0.32 [0.09, 1.07]
Garey 2006	6	176	141	1872	31.5%	0.43 [0.19, 1.00]
Total (95% CI)		**1154**		**2676**	**100.0%**	**0.24 [0.13, 0.44]**
Total events	27		207			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 4.56$, df = 3 (P = 0.21); $I^2 = 34\%$

Test for overall effect: Z = 4.55 (P < 0.00001)

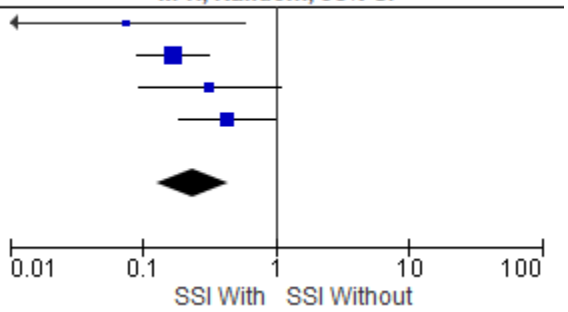
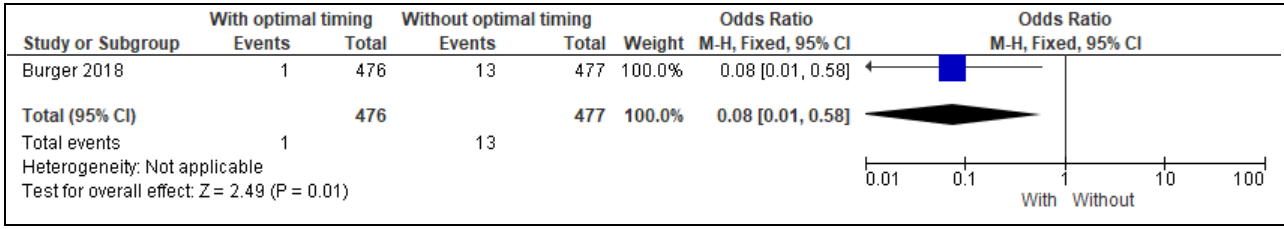


Figure 2. Comparison of surgeries with optimal timing of preoperative antibiotics versus surgeries without optimal timing of preoperative vancomycin, Outcome: SSI

Burger et al. (2018)

Characteristics of Study	
Methods	**Retrospective Cohort**
	Participants: Adult orthopedic patients **Setting:** Academic medical center **Number enrolled into study:** *N* = 1997 • Group 1: Treated with cefazolin alone, *n* = 1044 • Group 2: Treated with cefazolin plus vancomycin *n* = 953 o Vancomycin initiated at least 45 minutes prior to incision, *n* = 476 o Vancomycin initiated less than 45 minutes prior to incision, *n* = 477 **Gender, males (as defined by researchers):** 42% **Race / ethnicity or nationality (as defined by researchers):** • Not reported, the study occurred in the USA. **Age, mean, (SD):** 59.7 years **Inclusion Criteria:** • Total joint arthroplasty (knee or hip) and received o First generation cephalosporin o First generation cephalosporin with vancomycin **Exclusion Criteria:** • Received clindamycin as primary antibiotic • Received vancomycin alone • Dual antibiotic prophylaxis with first generation cephalosporin and gentamicin **Covariates identified:** o Physician antibiotic preference o Vancomycin dose was not adjusted for patient size o Use of antibiotic cement
Interventions	• This reports on the cephalosporin with vancomycin groups only o Cephalosporin with vancomycin initiated at least 45 minutes prior to incision o Cephalosporin with vancomycin initiated less than 45 minutes prior to incision
Outcomes	• **Primary outcome(s):** *Prosthetic joint infection • **Secondary outcome(s):** Not reported • **Safety outcome(s):** Not reported • *Outcomes of interest to the CMH CAT development team
Results	

Date Developed: August 12, 2020

If you have questions regarding this CAT – please contact Kelly Fehlhafer, RN, BSN, MBA, CNOR on behalf of the Surgical Site Infection Improvement Team or Lisa Schroeder MD.

	Note: • Optimal time defined as vancomycin initiated at least 45 minutes prior to incision **Limitations:** • Selection bias as physicians self-selected antibiotics • Patients deemed at risk more likely to get dual antibiotic regimen

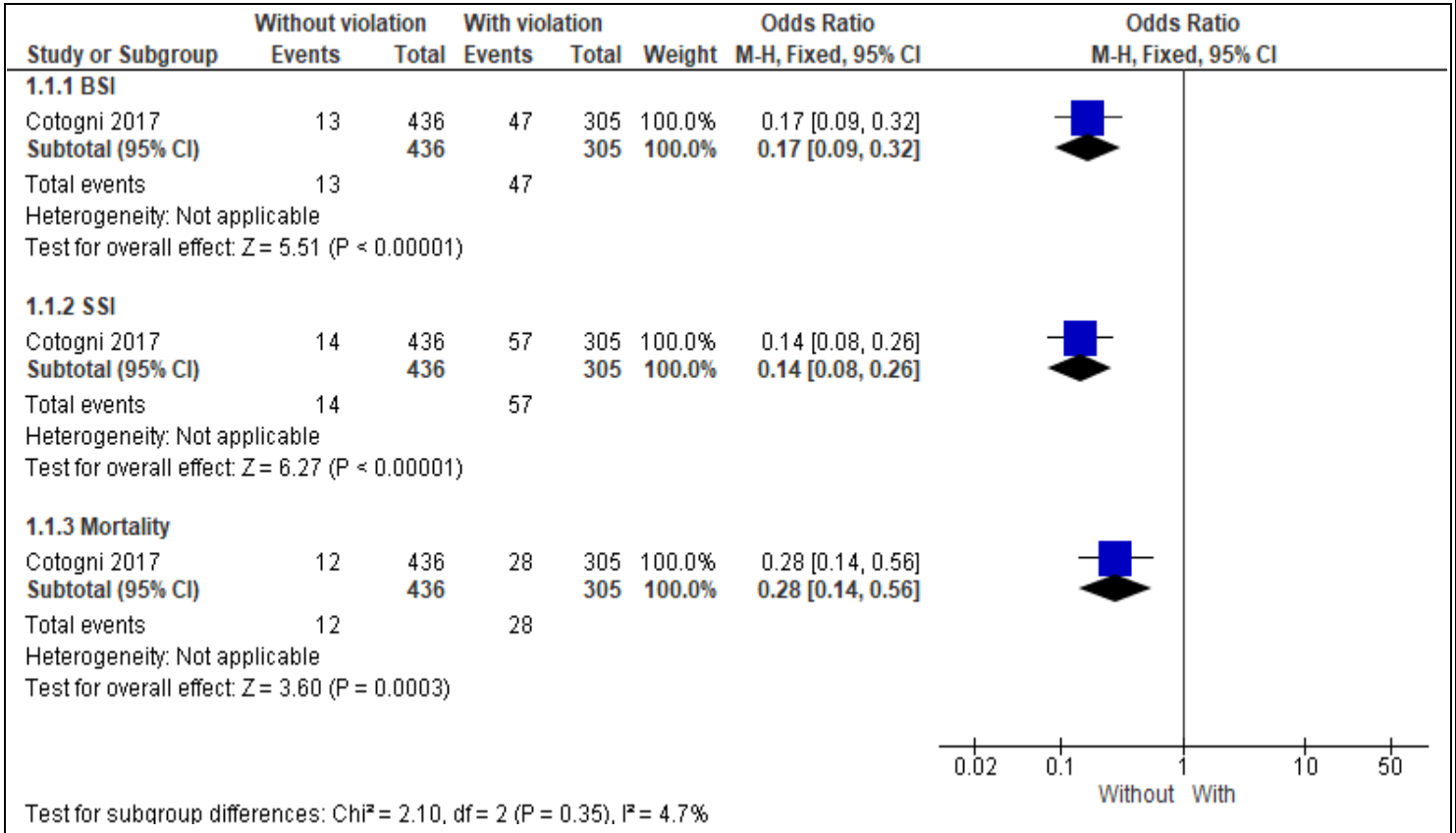
Cotogni et al. (2017)

Characteristics of study	
Methods	**Prospective Cohort**
Participants	**Participants:** Adults undergoing cardiovascular surgery **Setting:** Adult hospital, Italy **Consecutive enrollment:** *N* = 741 • **Group 1.** Without protocol violation, *n* = 436 • **Group 2,** With protocol violation, *n* = 305 **Completed Study:** *N* = 741 • **Group 1.** Without protocol violation, *n* = 436 • **Group 2,** With protocol violation, *n* = 305 **Gender, males (as defined by researchers):** • **Group 1:** *n* = 273 (63%) • **Group 2:** *n* = 174 (57%) **Race / ethnicity or nationality (as defined by researchers):** • The study occurred in Italy. The authors did not identify race or ethnicity of the participants. **Age, median in years, (range)** • **Group 1:** 70 (25-88) • **Group 2:** 70 (34-88) **Inclusion Criteria:** • Only exclusion criteria reported **Exclusion Criteria:** • Renal dysfunction, on dialysis or creatinine clearance ≤ 30 mL/min • Infectious disease that required antibiotic therapy in the last 2 weeks • Heart and lung transplant surgery • Solid or hematologic tumor • Chemotherapy or radiation therapy in the last 6 months • Taken to surgery from an intensive care unit • Allergy to cefazolin or vancomycin • Emergency surgeries
Interventions	**Both: Antimicrobial prophylaxis** • A single dose 1,000 mg cefazolin dose diluted in 20 mL of 0.9% sodium chloride initiated 30 to 60 minutes prior to surgery as a slow intravenous bolus, • A single 1,000 mg vancomycin dose, diluted in 100 mL 0.9% sodium chloride started 2 hours prior to surgery • Cohorts stratified by protocol violation defined as incision occurred before the completion of vancomycin infusion o Did not violate the timing protocol, i.e. incision after vancomycin infusion complete o Did violated the timing protocol, i.e. incision occurred prior to completion of vancomycin infusion

Outcomes

- *Infectious complications
- Mortality

Results



Comparison: With optimal timing vs. Without optimal timing, Outcome: Infections

Notes

SSI definition:

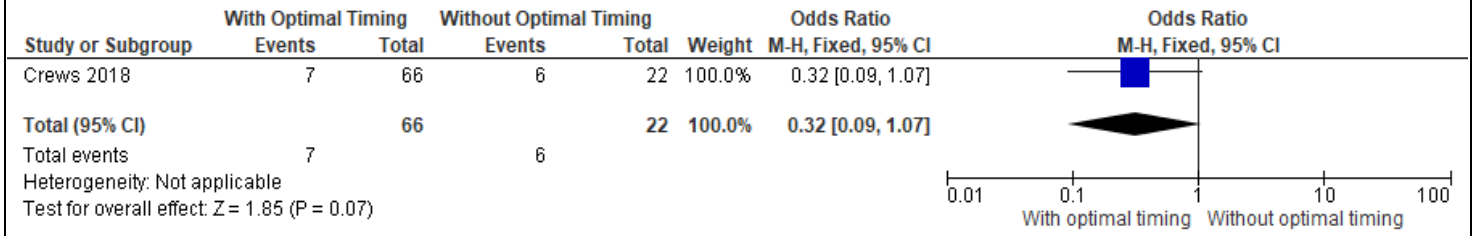
- One of the following is met
  - Superficial infection- above the sternum, no bone involvement
  - Deep infection- sternum and organ space such as mediastinum
  - Leg/ donor site
- Other, using CDC definitions, followed for 30 days after surgery
  - Blood stream infections
  - Mortality
- Patients at high risk with protocol violation had a higher occurrence of SSIs ($p < .001$) and mortality ($p < .001$) versus patients at high risk without protocol violation
- The logistic regression analysis showed increased risk for SSI occurrence for:

	o Mammary artery use (p = .025) o Surgical time (p < .001) o Intensive care unit (ICU) length of stay (p = .002) o High risk of developing SSIs (p < .001) o *Protocol violation (p < .001) o Age (p = .003)

Crews et al. (2018)

Characteristics of study	
Methods	Nested case control study
Participants	**Participants:** Children undergoing surgery of vertical expandable prosthetic titanium rib (VEPTR) implant or revision **Setting:** Children's hospital, USA **Enrollment:** *N* = 88 • **Group 1:** Cases, those who underwent surgery and developed at least one SSI, *n* = 22 • **Group 2:** Controls, those who underwent surgery and did not develop an SSI *n* = 66 • For each case three control subjects were randomly selected **Completed Study:** *N* = 88 • **Group 1:** Cases, *n* = 22 • **Group 2:** Controls, *n* = 66 **Gender, males (as defined by researchers):** • **Group 1:** Cases, 16 (72.7%) • **Group 2:** Controls, 31 (47%) **Race / ethnicity or nationality (as defined by researchers):** **Age, mean, (IQR) in years** • **Group 1:** Cases, 7.1 (5-10) • **Group 2:** Controls, 8.1 (6-11)

Interventions	**Both:** All underwent either VEPTR or VEPTR revision. Operative debridement with irrigation was universally performed. Two antibiotic timing intervals were employed. Data were analyzed comparing if interval was met or not met.
	• Standard interval- antibiotic administration 1 to 60 minutes prior to surgical incision
	  o Vancomycin could be administered within 120 minutes of incision
	• Strict interval- antibiotic administration 1 to 30 minutes prior to surgical incision
	  o Vancomycin could be administered within 60 minutes

Outcomes	• SSI
Results	 Comparison: With optimal timing vs. Without optimal timing, Outcome Infections

Notes	**Appropriate antibiotic dosing defined as** • ≥ 20 mg/kg of cefazolin, ≥ 10 mg/kg vancomycin or ≥ 10 mg/kg of clindamycin

Garey et al. (2006)

Characteristics of Study	
Methods	**Prospective Observational Cohort**
Participants	**Participants:** Cardiovascular surgery – CABG or valve replacement **Setting:** Tertiary care medical center, USA. **Number enrolled into study:** *N* = 2048 **Gender, males (as defined by researchers):** 68% **Race / ethnicity or nationality (as defined by researchers):** • Caucasian – 53% • African American – percent not reported • Hispanic – percent not reported • Other – percent not reported **Age, Years, Mean, SD:** • 64 ± 12 **Inclusion Criteria:** • Patients who underwent CABG or valve replacement surgery June 2002 to June 2005 **Exclusion Criteria:** • Infection due to infection related diagnosis such as endocarditis • Underwent previous cardiac surgery withing the previous year • Did not receive vancomycin **Covariates identified:** • Sex • Underlying diseases • Surgery type
Interventions	• Patients were assigned to one of 5 groups o **Group 1,** Vancomycin started 0-15 minutes prior to incision: *n* =15 (0.73%) o **Group 2,** Vancomycin started 16-60 minutes prior to incision: *n* =176 (8.6%) o **Group 3,** Vancomycin started 61-120 minutes prior to incision: *n* =888 (43.4%) o **Group 4,** Vancomycin started 121 – 180 minutes prior to incision: *n* =700 (34.2%) o **Group 5,** Vancomycin started > 180 minutes prior to incision: *n* =269 (13.1%)
Outcomes	**Primary outcome(s):** • *Rates of SSI **Secondary outcome(s):** • Not reported **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CAT development team
Results	**Results:** • Compared with receiving vancomycin 16 – 60 minutes prior to first incision o The odds of infection of those who received vancomycin ▪ 0-15 minutes prior: *OR* = 11.6, *p* = .001, 95% CI [2.6, 52.4] ▪ 61-120 minutes prior: *OR* = 2.3, NS, 95% CI [0.98, 5.61]

	▪ 121-180 minutes prior: *OR* = 2.6, *p* = .037, 95% CI [1.1, 6.2] ▪ > 180 minutes prior: *OR* = 2.1, NS, 95% CI [0.82, 5.62] o Sensitivity analysis controlling for start time of surgery (first case vs. other), age, gender, underlying disease, and surgery type had little or no effect on infection rate. **Limitations:** • Nonrandomized, selection bias a concern, but sensitivity analysis showed group assignment reliable • Unable to stratify to SSI type, superficial, deep, or organ space

Garey et al. (2008)

Characteristics of Study	
Methods	**Prospective Observational Cohort**
	Participants: Cardiovascular surgery – CABG or valve replacement **Setting:** Tertiary care medical center, USA. **Number enrolled into study:** *N* = 1666 • **Group 1,** Appropriate timing**:** *n* = 928 • **Group 2,** Inappropriate timing *n* = 738 **Gender, males (as defined by researchers):** 69% **Race / ethnicity or nationality (as defined by researchers):** • Only report % Caucasian – 71% • Other race/ethnicities included, but not reported, African American, Hispanic, Other **Age, Mean, SD:** 65 ± 12 **Inclusion Criteria:** • Patients who underwent CABG or valve replacement surgery January 2004- December 31, 2005 **Exclusion Criteria:** • Infection due to infection related diagnosis such as endocarditis • Did not receive vancomycin • Greater than one medication for antibiotic prophylaxis **Covariates identified:** • Sex • Underlying diseases • Surgery type
Interventions	• Patients were assigned to one of 4 groups o Vancomycin infusion began o 0-15 minutes before incision o 16-60 minutes before incision o 61-120 minutes before incision o > 120 minutes before incision • Groups 2 and 3 were considered appropriate timing • Groups 1 and 4 were considered inappropriate timing
Outcomes	**Primary outcome(s):** • *Length of stay in hospital • Length of stay in ICU • *Total hospital costs **Secondary outcome(s):** • Not reported **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CAT development team

Results

Results:

Difference in LOS, ICU LOS, and Cost			
Antibiotic Timing	LOS Hospital (days)	LOS ICU (days)	Total Hospital Costs (USD)
Appropriate timing (*n* = 928)	9 (7-14)	2 (1-4)	25,321 (19,429-35,471)
Inappropriate timing (*n* = 738)	10 (8-17)	3 (2-6)	29,475 (21,507- 46,46,488)

Note: Median (interquartile range)

Limitations:

- A small number of patients (*n* = 156) who received vancomycin in the 16-60 minutes time prior to incision did not allow for sub-analysis for this tighter time frame. Results reported are for 16-120 minutes prior to incision.

Malhotra et al. (2020)

Characteristics of Study-	
Methods	Quality report - goal was to improve vancomycin infusion start time, not reduce SSI
	Participants: All surgical patients eligible **Setting:** Teaching hospital, USA **Number enrolled into study:** *N* = 33,475 • Received vancomycin, n = 7,392 • Received cefazolin n = 26,065 **Gender, males (as defined by researchers):** Not reported **Race / ethnicity or nationality (as defined by researchers):** • The study occurred in the USA. The authors did not identify race or ethnicity of the participants. **Age, mean/median in months/years, (range/IQR):** Not reported **Inclusion Criteria:** • All patients undergoing a surgical intervention • Received cefazolin or vancomycin or multiple antibiotics • November 1, 2014 to October 31, 2015 **Exclusion Criteria:** • Received antibiotics other than cefazolin, vancomycin or multiple antibiotics • Surgical services with low frequency of vancomycin utilization (patient count less than 5) **Covariates identified:** Not reported
Interventions	Compared infection rates for patients who received antibiotics: o Standard or compliant ▪ Cefazolin 0-60 minutes prior to incision ▪ Vancomycin 60-120 minutes prior to incision o Non-compliant ▪ Outside ranges above
Outcomes	**Primary outcome(s):** • *Timing of vancomycin infusion **Secondary outcome(s):** • Not reported **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CAT development team
Results	**Results:** • Vancomycin start time in minutes, mean: 51.45 ± 33.58 • Percent of time national vancomycin timing standards were met, *n* = 2,665 (36.05%) • SSI • Infection rate if cefazolin or vancomycin infused within national timing standards 0.49% and 0.66% respectively, *p* = 0.768, *NS* • Odds of infection when vancomycin infusion started: • Between 60 and 120 minutes prior to incision *OR* = 1.4, *p* = .027, 95% CI [0.75, 2.73]

	• No later than 15 minutes from incision, *OR* = 4.23, *p* < .001, 95% CI [2.32, 7.74] • No later than 25 minutes from incision, *OR* = 3.16, *p* < .001, 95% CI [1.77, 5.66] • Any antibiotic infused < 25 minutes prior to incision predicted SSI, *OR* = 3.162, 95% CI [1.756, 5.663] • Costs – • Subgroup analysis of a matched cohort (*n* = 88) of patients who had vancomycin administration too close to incision and SSI, versus those with standard infusion time without SSI • 3.47 million USD higher total cost of care, *p* <.001 (208% of standard infusion time and no SSI) • The daily cost of care was also dramatically increased (342% of the daily cost of care vs uninfected patients, *P* < 0.001) **Limitations:** • All patients undergoing surgery included. Differences surgery type not differentiated • For the cost analysis, although patients were well matched, disease specific factors may influence the difference in hospital costs.

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