TITLE: **The Timing of Prophylactic Antibiotics for Surgery: A Review of the Clinical Evidence**

DATE: 26 February 2013

CONTEXT AND POLICY ISSUES

A surgical site infection (SSI) is a complication of surgery. The World Health Organization defines a SSI as any purulent discharge, abscess, or spreading cellulitis at the surgical site occurring up to a month after the operation.[1] The risk of developing a SSI depends on various factors including type of surgical procedure and patient co-morbidities.[2]

Surgical site infections occur in approximately 3% of surgeries overall, but range from 2% in clean surgical sites to 10% in dirty surgical sites.[3] Surgical site infections are associated with increased patient morbidity and economic consequences to the health care system.[3] The average length of hospitalization for patients with SSIs is approximately 6.5 days longer than for patients without SSIs.[3]

Measures to prevent SSI include limiting the preoperative hospital stay, preoperative shower and local skin preparation of the patient, and antibiotic prophylaxis.[1] Prophylactic antibiotic administration reduces the burden of microorganisms at the surgical site and thereby decreases the risk of wound contamination.[4,5] The efficacy of antibiotic prophylaxis is well established in situations of high risk of infection or when the occurrence of an infection would have grave consequences for the patient (for example when the patient is immunocompromised).[5] The appropriate timing of antibiotic therapy pre-operatively allows for adequate blood and tissue concentrations. Administration of antibiotics within one hour (for cephalosprorins for example) to two hours (for vancomycin for example) before the surgical incision translates in lower rates of SSIs than if the antibiotics are administered more than two hours before surgery.[5] If this therapeutic window is not feasible, antibiotics administered 30 to 60 minutes prior to surgery may be more effective than if administered immediately before the surgery.[5]

This report will review the clinical evidence on the appropriate timing of antimicrobial prophylaxis administered pre-operatively.

RESEARCH QUESTION

What is the clinical evidence on the administration of antibiotics at 0 to 14 minutes, 15 to 60 minutes, and 61 to 120 minutes prior to incision during surgery?

KEY FINDINGS

From limited evidence, a trend was seen between timing of prophylactic antibiotic administration and infection risk. There was a lower risk of infection when surgical antibiotic prophylaxis was administered 30 to 60 minutes pre-operatively. This finding requires confirmation in well-designed trials.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, The Cochrane Library (2012, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and January 29, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients undergoing surgery (e.g., abdominal surgery, orthopedic surgery) Subgroup: pediatric patients
Intervention	Cefazolin, cefuroxime, vancomycin, ciprofloxacin, levofloxacin
Comparator	None specified
Outcomes	Infection rate
Study Designs	Heath Technology Assessment/ Systematic review/ Meta-analysis; RCTs, and non-RCTs

RCTs=randomized controlled trials

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2008, or were duplicate publications of the same study.

Critical Appraisal of Individual Studies

The methodological quality of non-RCTs was assessed using the Downs and Black checklist.[6] A numeric score was not calculated and the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 185 citations. Upon screening titles and abstracts, 29 potentially relevant articles were retrieved for full-text review. Upon consulting other sources, 7 relevant reports were retrieved. Of the 36 potentially relevant articles, 5 non-RCTs met the inclusion criteria and 4 were included in this review. One trial was a duplicate publication.[7] The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Four observational trials were retrieved and are described in Appendix 2. There were three large prospective observational trials[8-10] and one retrospective chart review.[11] None of the trials included a control group. The main outcome for all four trials was the rate of SSI. All trials provided results on sub-groups of patients divided according to timing of administration of antibiotics.

An American group conducted a trial that considered data from consecutive patients who received cefuroxime (n=24,272) or vancomycin (n=4,430) prior to cardiac surgery and for 2 doses post-surgery.[8] The data was collected over 13 years. Length of follow-up to ascertain a SSI was the duration of the hospitalization following surgery. SSI was specific to sternal wound infection as defined by The Society of Thoracic Surgeons. The patients had various co-morbidities including COPD, peripheral artery disease, diabetes, and large BMI. It is unclear how the results were adjusted for confounders.

Another US observational trial randomly collected information on a group of patients undergoing cardiac surgery, hysterectomy, or arthroplasty of the hip or knee at 29 centres, including both teaching and non-teaching hospitals (n=4,472).[9] Patients were administered a cephalosporin alone or in combination with vancomycin, vancomycin alone, a fluoroquinolone, or other antibiotics with short infusion times, pre-operatively and continued 24 to 48 hours post-operatively. Length of follow-up to ascertain a SSI was three to nine months. All hospitals used the National Nosocomial Infections Surveillance system definition for SSI. Patient co-morbidities were not described; the study results were adjusted for duration of surgery and procedure type.

A Swiss prospective trial considered all consecutive general surgeries (72% of patients had clean operations) occurring over two years (n=3,312).[10] Patients received cefuroxime as a single dose before incision. Colorectal patients received metronidazole in addition to the cefuroxime. Length of follow-up was 30 days post-surgery or one-year if the patient had received an implant. All cases with a SSI were validated by an infectious disease specialist. The patients had various co-morbidities such as diabetes, and large BMI. It is unclear how the results were adjusted for confounders.

One US retrospective chart review randomly selected cases of patients who had undergone colorectal surgery from a database (n=605).[11] The antibiotics administered prophylactically included metronidazole in combination with cefazolin, ciprofloxacin or levofloxacin, cefotoxin alone, and other antibiotics. Greater than 70% of patients received cefazolin with metronidazole or cefoxitin alone. Antibiotic therapy was continued 24 hours post-operatively. SSIs were considered up to 30 days following surgery. SSI was defined by the Center for Disease Control (CDC) criteria. The majority of patients' operations (94%) were of the clean-contaminated type. Co-morbidities included coronary artery disease, hypertension, diabetes, and COPD. The study was adjusted for confounders, including co-morbidities. Standard practice at the institution where the trial took place dictates the use of mechanical bowel preparation in elective cases; however this was not consistently documented and was not considered in the study.

Summary of Critical Appraisal

Individual study strengths and limitations are presented in Appendix 3. All trials clearly described their objective and the criteria used to define SSIs. Inclusion and exclusion criteria were well described. Two trials clearly described the patient characteristics.[8,11] One trial[9] excluded patients with missing data but did not report their characteristics. None of the trials included a control group, although sub-groups were compared based on timing of antibiotic administration. Antibiotic doses were not specified in two trials.[9,11] All four trials had different criteria to define SSIs and conducted the trials in different surgical populations. Other infection control interventions (for example pre-operative skin cleansing, surgical hair removal) which may have affected the study results were not described in three trials.[8-10] Confounders were clearly specified in two trials,[9,11] although the study by Steinberg et al.[9] only included two confounders in the analysis. Weinberg et al.[10] adjusted the analysis for 12 confounders but did not specify what they were.

Summary of Findings

Details of the results of the four trials are available in Appendix 4.

In Koch et al.,[8] the predicted percentage of infection was the lowest when cefuroxime was administered 30 minutes prior to the surgical incision (1.9%) and highest at 75 minutes (3.7%). The mean time at which cefuroxime administration resulted in the lowest likelihood of SSI was 27 minutes (± standard deviation 14 minutes) but this could change depending on risk factors such as chronic obstructive pulmonary disease (COPD) or increased body mass index (BMI). For example COPD patients had a mean optimal timing of 18 minutes compared to 30 minutes for patients without COPD. The administration of cefuroxime at the optimal time of 27 minutes could result in a 9.5% reduction in post-operative sternal wound infection.

Similarly, the predicted percentage of infection was the lowest when vancomycin was administered 30 minutes prior to the surgical incision (1.8%) and highest at 75 minutes (4.6%). The mean time at which vancomycin administration resulted in the lowest likelihood of SSI was 32 minutes (± standard deviation 10 minutes) but this could change depending on risk factors such as increased BMI. For example, higher BMI patients had a mean optimal timing of 39 minutes compared to 29 minutes for patients with lower BMI. The administration of vancomycin at the optimal time of 32 minutes could result in an 18% reduction in post-operative sternal wound infection.

In Steinberg et al,[9] the overall association between timing and infection risk was statistically significant (P = 0.04). When antibiotics were administered 30 minutes pre-operatively for cephalosporins and within 60 minutes pre-operatively for vancomycin or the fluoroquinolones, the risk of infection was 2.1%. Whereas administering the antibiotics earlier than recommended by guidelines (as referred to in the study) increased the risk of infection to 2.8% but this finding was not statistically significant [adjusted odds ratio (OR) 1.3, 95% confidence interval (CI): 0.7 to 2.4].

When only cephalosporins were considered in the analysis, the lowest risk of infection was seen with their administration 30 minutes or less before the incision (1.6%). The infection risk was highest (4.7%) when the cephalosporin was administered more than two hours before surgery or not administered at all, but this finding was not statistically significant [adjusted OR 2.1, 95% CI: 0.68 to 6.59]. The number of observations using vancomycin or fluoroquinolones was too small to conduct analyses specific to these antibiotics.

In Weber et al,[10] the overall SSI rate was 4.7%. Various analyses were presented based on different comparisons of time intervals. One analysis compared patients who had received cefuroxime (± metronidazole) less than 30 minutes prior to incision to patients whose administration varied between 30 to 120 minutes before incision. This latter group was associated with a statistically significant increase in risk of infection [adjusted OR 1.7, 95% CI: 1.2 to 2.3]. A second analysis divided the cohort of patients into three groups: patients who had received an antibiotic less than 30 minutes prior to incision, patients whose administration varied between 30 to 59 minutes, and patients whose administration varied between 60 to 120 minutes before incision. The lower risk of infection was seen in the group of patients administered the antibiotic at 30 to 59 minutes pre-incision. The other two groups had a statistically higher risk of infection. Finally, the third analysis divided the intervals into 15-minute increments. The lowest risk of infection (2.4%) was obtained when the antibiotic was administered 45 to 59 minutes prior to surgery. The infection risk was highest (7.5%) and statistically significant at 75 to 120 minutes [adjusted OR 3.2, 95% CI: 1.4 to 7.0].

In Ho et al,[11] the overall SSI rate was 21.5%. The early administration of the initial dose of antibiotics (more than 30 minutes before the incision) was associated with a higher risk of SSI although statistical significance was borderline [adjusted OR 1.7, 95% CI: 1.0 to 3.0].

Limitations

In three of the four trials, antibiotics were administered prophylactically post-operatively for 24 to 48 hours as per accepted standards.[8,9,11] This is a major confounder that was unaccounted for in the analyses and which may have changed the incidence of SSIs if doses were missed post-operatively or if antibiotics were substituted post-operatively for an agent in another class.

Another major limitation is that in two trials,[8,11] the study period spanned several years. During this time, there may have been institutional changes in infection control or in pattern of microbial resistance for example which may have impacted the results.

Although two trials adjusted their analysis for confounders, there may be unmeasured confounding variables which would affect the study results.

Two trials had an inappropriate length of follow-up.[8,9] Koch et al [8] limited the follow up to the time of hospitalization, whereas in Steinberg et al[9] the duration of follow up was three to nine

months. Although the trials did not specify the number of patients who received implants, incident cases of SSI may have been missed in implant patients for which the risk of SSI is a possibility up to one year after surgery.

In all four trials, the absolute risk of infection was low as seen in the number of reported events (<75). As such, the low number of cases limits statistical power and increases our uncertainty of the results.

Generalizability of the trial results need to be considered in light of the following: The optimal time window for surgical antibiotic prophylaxis described in the included trials may not be generalizable to patients presenting with co-morbidities. Also, the trials were conducted in specific types of surgeries and the findings may be applicable only to these. For example none of the trials were conducted in patients undergoing neurosurgeries or head and neck surgery. Although cephalosporins are the antibiotics of choice for many types of surgeries, the trials did not consider other types of antibiotics that could be administered as prophylaxis, for example clindamycin with or without aminoglycosides.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Four observational trials on the timing of surgical antibiotic prophylaxis were identified. It was shown that there is an association between timing of administration of antibiotics and surgical infection rates. Administering the antibiotics earlier than recommended by guidelines (as defined by the trials) increased the risk of infection. Administering antibiotics 30 to 60 minutes prior to incision was optimal and administration less than 30 minutes or more than 2 hours before surgery increased the risk of infection.

However, the results need to be interpreted in light of the fact that the trials were observational studies. This represents a lower level of evidence and well-designed RCTs are required to confirm these findings. Other limitations include the fact that all trials defined SSIs differently; the data collection was done over several years in two trials and changes in infection control or in pattern of microbial resistance could have occurred; length of follow-up was inappropriate in two trials; and there may be unmeasured confounding variables as for all observational trials. Furthermore, the findings may only be generalizable to the types of procedures or antibiotics specific to the trials. Patient-specific factors such as BMI or pre-existing morbidities are also important considerations in the interpretation of the results.

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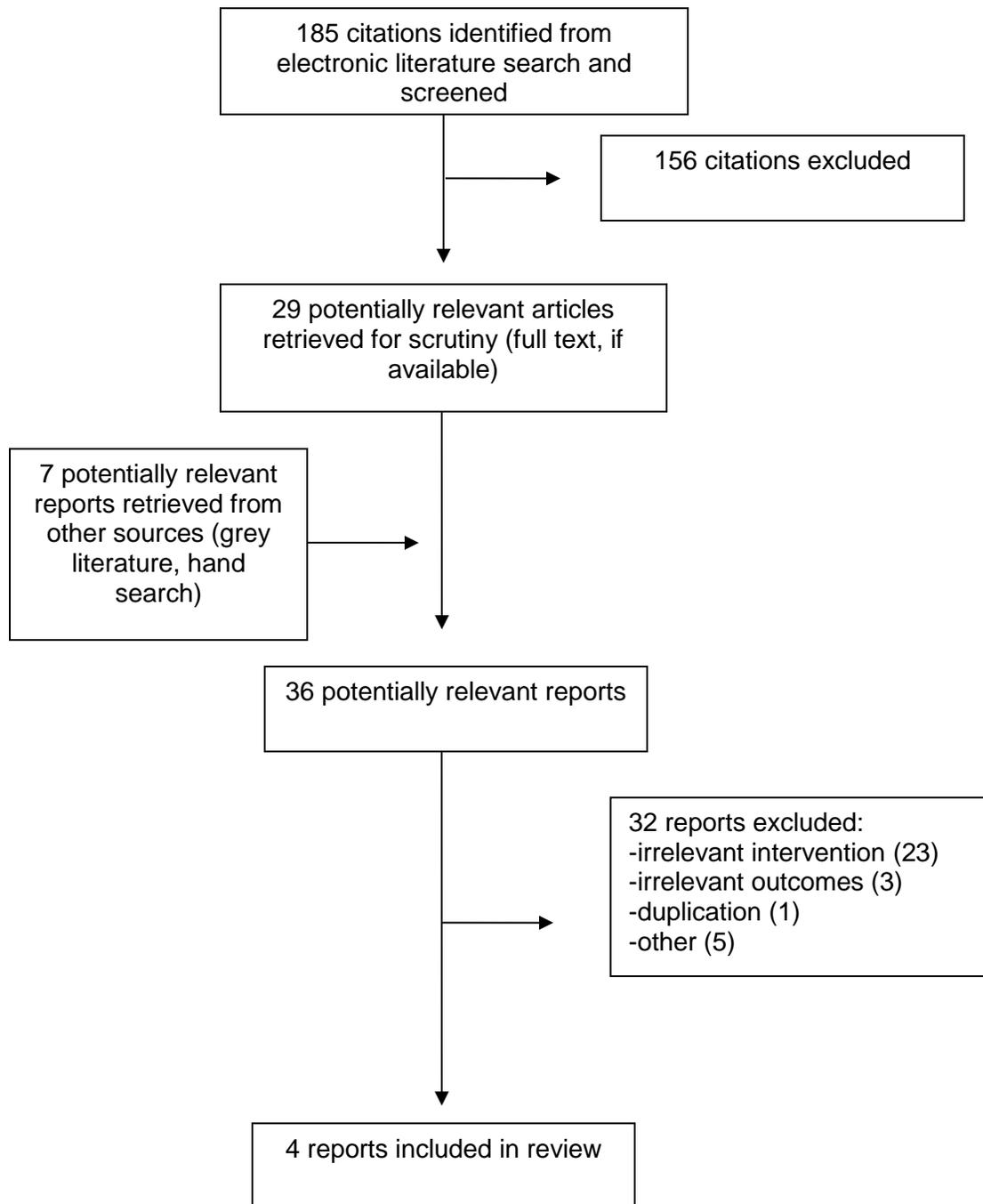Canadian Agency for Drugs and Technologies in Health
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www.cadth.ca

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APPENDIX 1: Selection of Included Studies

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│ electronic literature search and│
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Appendix 2: Characteristics of Included Studies

Characteristics of Included Studies				
First Author, Year, Country,	Study Design	Intervention(s)	Included patients	Main comparative clinical outcomes reported
Koch 2012[8] USA	Prospective observational study N=28,250 (28,702 procedures)	Cefuroxime 1.5 g IV 60 min before incision (n=24,272) or vancomycin 120 min before incision for penicillin allergic patients (n=4,430). Both were administered post-operatively q12h for 2 doses.	Patients undergoing cardiac surgery	Rate of deep and superficial sternal wound infection identified during the primary hospitalization
Ho 2011[11] USA	Retrospective chart review – cases randomly selected from a database N=605	Cefazolin + metronidazole; cefotoxin; levofloxacin + metronidazole; ciprofloxacin + metronidazole; others. Antibiotics were continued 24 h post-op.	Patients undergoing elective colorectal surgery	Incidence of SSI Identified at least 30 days following the surgery
Steinberg 2009[9] USA	Multicenter (n=29), prospective observational study – cases randomly selected N=4,472	Cephalosporin (n=3,405); cephalosporin + vancomycin (n=575); vancomycin (n=218); fluoroquinolone (n=240); no SAP (n=34). Antibiotics were continued 24-48 h post-op.	Patients undergoing cardiac surgery, hysterectomy, or hip/ knee arthroplasty	Occurrence of SSIs; follow-up was 3 to 9 months
Weber 2008[7,10] Switzerland	Prospective observational study N=3,313 (3,836 procedures)	Cefuroxime 1.5 g IV (combined with metronidazole 500 mg IV for colorectal patients) administered as a single dose before incision.	Patients undergoing general surgery	Rate of SSI 30 days post-surgery (one year if implant surgery)
IV=intravenous; min=minutes; q12h=every 12 hours; SSI=surgical site infection				

Appendix 3: Summary of Critical Appraisal of Included Studies

Summary of Critical Appraisal of Included Studies		
First Author, Publication Year	**Strengths**	**Limitations**
Koch 2012[8] USA	• objective of study clearly described • main outcome clearly described and valid • patient characteristics clearly described • interventions clearly described • missing data imputed using Markov Chain Monte Carlo • cohort representative of cardiac surgical patients	• antibiotics continued post-operatively • length of follow-up restricted to hospitalization and SSI occurring after discharged not included • data spans 13 years • not clear how the results were adjusted for confounders • number of patients in each time intervals not reported • number of events in each time intervals not reported • percentage of infections at different time intervals reported but do not report effect size such as odds ratios; no reference group
Ho 2011[11] USA	• objective of study clearly described • main outcome clearly described and valid • patient characteristics clearly described • confounders specified • cohort identified through random selection • cohort representative of colorectal surgical patients • length of follow-up to detect SSI specified and valid	• antibiotic doses not specified • antibiotics continued post-operatively • not clear how missing data was handled • data spans 7 years • method of bowel preparation not specified • number of events not reported
Steinberg 2009[9] USA	• objective of study clearly described • main outcome clearly described and valid • centres characteristics well described • cohort identified through random selection • confounders specified • analysis was adjusted for type of surgery	• antibiotic doses not specified • antibiotics continued post-operatively • patients with missing data excluded • analysis adjusted for two confounders only • patient characteristics not well described • number of events was <50 per sub-group • multicenter study (differences in post-discharge follow-up) • follow-up too short for patients with implants
Weber 2008[7,10] Switzerland	• objective of study clearly described • main outcome clearly described and valid • overall patient characteristics described • length of follow-up to detect SSI specified and valid • analysis adjusted for 12 confounders only	• patients who received antibiotics outside a 2 hour window before surgery were excluded • patient characteristics not described by type of surgery • confounders not specified • unclear as to whether or not analysis was adjusted for type of surgery (different types of surgeries would have variable risk for developing a SSI) • number of events was <75 per sub-group

Appendix 4: Main Study Findings and Authors' Conclusions

Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
Koch 2012[8] USA	Cefuroxime group: Predicted percentages of infection was 2.0% at incision 1.8% at 15 min before incision 1.9% at 30 min before incision 2.2% at 45 min before incision 2.8% at 60 min before incision 3.7% at 75 min before incision Time at which cefuroxime administration resulted in the lowest likelihood of SSI: mean 27 min ± sd 14 min Vancomycin group: Predicted percentages of infection was 2.6% at incision 2.1% at 15 min before incision 1.8% at 30 min before incision 2.2% at 45 min before incision 3.2% at 60 min before incision 4.6% at 75 min before incision Time at which vancomycin administration resulted in the lowest likelihood of SSI: mean 32 min ± sd 10 min	*Optimal timing with consideration of patient-specific risk factors reduced the likelihood of developing postoperative sternal wound infections.* (p937)
Ho 2011[11] USA	Administration of the initial dose of antibiotics >30 min before incision: Unadjusted OR=1.7 (95% CI: 1.1, 2.6), p<0.05 Adjusted* OR=1.7 (1.0, 3.0). *Adjusted for: disease, year, surgeon experience, transfusion, wound class, type of surgery, history of radiation, serum albumin concentration, co-morbidities, intraoperative hypotension, intraoperative hypothermia, postoperative glycemic control, and ICU admission.	*…proper timing of administration is crucial to limit SSIs in elective abdominal colorectal surgery with intestinal anastomosis.* (p259)
Steinberg 2009[9] USA	Group 1: cephalosporins administered within 30 min of incision or vancomycin/ fluoroquinolones administered within 60 min of incision Infection risk=2.1% (reference group) Group 2: cephalosporins administered within 31-60 min of incision or vancomycin/ fluoroquinolones administered within 61-120 min of incision Infection risk=2.4% Unadjusted RR of infection (95% CI)=1.16 (0.75, 1.79), p=0.5 Adjusted* OR for infection (95% CI)= 1.48 (0.92, 2.38), p=0.06 Group 3: SAP given earlier than guidelines recommendations Infection risk=2.8% Unadjusted RR of infection (95% CI)=1.36 (0.78, 2.36), p=0.3 Adjusted* OR for infection (95% CI)= 1.30 (0.70, 2.41), p=0.39 Cephalosporins only:	*…the number of observations using vancomycin was too small to assess optimal timing for vancomycin.* (p14) *…a consistent relationship between timing of prophylactic antibiotics and infection risk and show a trend toward lower risk when prophylaxis with cephalosporins and other antibiotics with short infusion times was given with 30 minutes prior to incision.* (p14)

Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
	>120 min before incision or no SAP Infection risk=4.7% Unadjusted RR of infection (95% CI)=2.54 (0.89, 7.21), p=0.07 Adjusted* OR for infection (95% CI)= 2.11 (0.68, 6.59) 61-120 min before incision Infection risk=2.4% Unadjusted RR of infection (95% CI)=1.49 (0.74, 3.00), p=0.26 Adjusted* OR for infection (95% CI)= 1.25 (0.57, 2.76) 31-60 min before incision Infection risk=2.4% Unadjusted RR of infection (95% CI)=1.48 (0.88, 2.50), p=0.13 Adjusted* OR for infection (95% CI)= 1.74 (0.98, 3.08) 0-30 min before incision (reference group) Infection risk=1.6% *Adjusted for duration of surgery and procedure type	
Weber 2008[7,10] Switzerland	Analysis #1 <u><30 min before incision (reference group)</u> 30 to 120 min before incision: Unadjusted OR=1.71 Adjusted* OR (95%CI)=1.66 (1.2, 2.3), p=0.002 Analysis #2 <u><30 min before incision:</u> Unadjusted OR=2.01 Adjusted* OR (95%CI)=1.95 (1.4, 2.8), p<0.001 30 to 59 min before incision (reference group) 60 to 120 min before incision: Unadjusted OR=1.75 Adjusted* OR (95%CI)=1.74 (1.0, 2.9), p=0.04 Analysis #3 0 to14 min before incision: Infection risk=4.7% Unadjusted OR (95%CI)=1.99 (1.0, 3.8), p=0.04 Adjusted* OR (95%CI)=1.75 (0.9, 3.4), p=0.1 15 to 29 min before incision: Infection risk=6.8% Unadjusted OR (95%CI)=2.96 (1.6, 5.5), p=0.001 Adjusted* OR (95%CI)= 2.82 (1.5, 5.3), p=0.001 30 to 44 min before incision: Infection risk=3.3% 45 to 59 min before incision (reference group) Infection risk=2.4% 60 to 74 min before incision: Infection risk=3.4%	*When cefuroxime is used as a prophylactic antibiotic, administration 59 to 30 minutes before incision is more effective than administration in the last half hour.[10] (p925)* *…administration of SAP within the final half hour before surgery may be too late for optimal prevention of SSI.[7] (p5)*

Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	75 to 120 min before incision: Infection risk=7.5% Unadjusted OR (95%CI)=3.25 (1.5, 7.1), p=0.003 Adjusted* OR (95%CI)= 3.16 (1.4, 7.0), p=0.005 *Adjusted for 12 potential confounders	
CI=confidence interval; ICU=intensive care unit; min=minutes; OR=odds ratio; RR=relative risk; SAP=surgical antimicrobial prophylaxis; sd=standard deviation; SSI=surgical site infection		