Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial

Walter P Weber, Edin Mujagic*, Marcel Zwahlen, Marcel Bundi, Henry Hoffmann, Savas D Soysal, Marko Kraljević, Tarik Delko, Marco von Strauss, Lukas Iselin, Richard X Sousa Da Silva, Jasmin Zeindler, Rachel Rosenthal, Heidi Misteli, Christoph Kindler, Peter Müller, Ramon Saccilotto, Andrea Kopp Lugli, Mark Kaufmann, Lorenz Gürke, Urs von Holzen, Daniel Oertli, Evelin Bucheli-Laffer, Julia Landin, Andreas F Widmer, Christoph A Fux, Walter R Marti*

Summary

Background Based on observational studies, administration of surgical antimicrobial prophylaxis (SAP) for the prevention of surgical site infection (SSI) is recommended within 60 min before incision. However, the precise optimum timing is unknown. This trial compared early versus late administration of SAP before surgery.

Methods In this phase 3 randomised controlled superiority trial, we included general surgery adult inpatients (age ≥18 years) at two Swiss hospitals in Basel and Aarau. Patients were randomised centrally and stratified by hospital according to a pre-existing computer-generated list in a 1:1 ratio to receive SAP early in the anaesthesia room or late in the operating room. Patients and the outcome assessment team were blinded to group assignment. SAP consisted of single-shot, intravenous infusion of 1·5 g of cefuroxime, a commonly used cephalosporin with a short half-life, over 2–5 min (combined with 500 mg metronidazole in colorectal surgery). The primary endpoint was the occurrence of SSI within 30 days of surgery. The main analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT01790529.

Findings Between Feb 21, 2013, and Aug 3, 2015, 5580 patients were randomly assigned to receive SAP early (2798 patients) or late (2782 patients). 5175 patients (2589 in the early group and 2586 in the late group) were analysed. Median administration time was 42 min before incision in the early group (IQR 30–55) and 16 min before incision in the late group (IQR 10–25). Inpatient follow-up rate was 100% (5175 of 5175 patients); outpatient 30-day follow-up rate was 88·8% (4596 of 5175), with an overall SSI rate of 5·1% (234 of 4596). Early administration of SAP did not significantly reduce the risk of SSI compared with late administration (odds ratio 0·93, 95% CI 0·72–1·21, p=0·601).

Interpretation Our findings do not support any narrowing of the 60-min window for the administration of a cephalosporin with a short half-life, thereby obviating the need for increasingly challenging SAP timing recommendations.

Funding Swiss National Science Foundation, Hospital of Aarau, University of Basel, Gottfried und Julia Bangerter-Rhyner Foundation, Hippocrate Foundation, and Nora van Meeuwen-Häfliger Foundation.

Introduction

Surgical site infections (SSIs) are the most common hospital-acquired infections in surgical patients, and have a substantial economic effect.[1] Administration of surgical antimicrobial prophylaxis (SAP) is a highly effective method that reduces the risk of SSI after various surgical procedures.[2–4] Single-shot first-generation or second-generation cephalosporins are widely used as the drug of choice for routine SAP, supplemented with metronidazole to provide anaerobic activity in colorectal surgery.[5]

The association between timing of SAP and risk of SSI has been described in early experimental animal studies.[6] The landmark study by Classen and colleagues[7] in 1992 showed that the lowest risk of SSI in human beings was when SAP was initiated within 2 h of skin incision. The 2016 WHO guidelines for the prevention of SSI still call for a timing of less than 120 min before incision, but recommend that administration should be closer to the incision time (<60 min before) for antibiotics with a short half-life, such as commonly used cephalosporins and penicillins.[8] This 60-min window before surgery reflects the most widely implemented recommendation on SAP timing.[5,9,10] The 2013 National Institute for Health and Care Excellence guidelines simply recommend a single dose of antibiotic intravenously on starting anaesthesia.[11]

Several groups have attempted to further reduce the 60-min window, resulting in two opposing clinical trends in SAP timing recommendations. Most of these observational studies favour the administration of SAP shortly before incision.[12–14] Therefore, some guidelines suggest that SAP should be administered within the final 30 min before incision, except for vancomycin and fluoroquinolones.[15,16] Other observational studies, including the largest prospective cohort study on cefuroxime (a second-generation cephalosporin) to date,[17,18] suggested that administration of SAP close to

Lancet Infect Dis 2017; 17: 605–14

Published Online April 3, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30176-7

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on October 20, 2017.

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*Contributed equally

Department of General Surgery, University Hospital Basel, Basel, Switzerland (Prof W P Weber MD, E Mujagic MD, H Hoffmann MD, S D Soysal MD, M Kraljević MD, T Delko, M von Strauss, L Iselin, J Zeindler, H Misteli MD, Prof L Gürke MD, U von Holzen MD, Prof D Oertli MD, J Landin MD); **University of Basel, Basel, Switzerland** (Prof W P Weber MD, E Mujagic, H Hoffmann, S D Soysal, M Kraljević, T Delko MD, M von Strauss MD, L Iselin MD, J Zeindler MD, Prof R Rosenthal MD, H Misteli, R Saccilotto MD, A Kopp Lugli MD, Prof M Kaufmann MD, Prof L Gürke MD, U von Holzen MD, Prof D Oertli, J Landin, Prof A Widmer MD); **Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland** (Prof M Zwahlen PhD); **Department of General Surgery, Hospital of Aarau, Aarau, Switzerland** (M Bundi MD, M von Strauss, R X Sousa Da Silva MD, Prof W R Marti MD); **Department of Anaesthesiology, Hospital of Aarau, Aarau, Switzerland** (Prof C Kindler MD, P Müller MD); **Department of Infectious Diseases, Hospital of Aarau, Aarau, Switzerland** (E Bucheli-Laffer MD,

C A Fux MD); **Department of Anaesthesiology, University Hospital Basel, Basel, Switzerland** (A Kopp Lugli, Prof M Kaufmann); **Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland** (Prof A Widmer MD); **and Department of Clinical Research, University Hospital Basel, Basel, Switzerland** (R Saccilotto), **Indiana University School of Medicine South Bend, Goshen Center for Cancer Care, Goshen, IN, USA** (U von Holzen MD) **Harper Cancer Research Institute, South Bend, IN, USA** (U von Holzen MD)

Correspondence to:
Prof Walter P Weber, Department of General Surgery, University Hospital Basel, Basel 4031, Switzerland
walter.weber@usb.ch

Research in context

Evidence before this study

In their 2016 global guidelines for the prevention of surgical site infection (SSI), WHO provides a strong recommendation based on moderate quality of evidence to administer surgical antimicrobial prophylaxis (SAP) within 120 min before incision. WHO recommend that administration should be closer to the incision time (<60 min) for antibiotics with a short half-life, such as commonly used cephalosporins and penicillins. In their summary of evidence, 13 observational studies including 53 975 adult patients were included; two studies were from multiple centres. No randomised controlled trials were identified. The guideline development group described this research gap and the need for further studies on this topic, and highlighted the scarce evidence available on optimal SAP timing to prevent SSI. The guideline development group stated that in particular and as a high priority, randomised controlled trials comparing the effect of different time intervals (ie, 30–60 min *vs* 0–30 min) for antibiotics with a short half-life are needed.

The 2013 National Institute for Health and Care Excellence guidelines simply recommend a single dose of antibiotic intravenously on starting anaesthesia. The 2014 Society for Healthcare Epidemiology of America and Infectious Diseases Society of America guidelines recommend administration within 1 h before incision, with superior efficacy between 0 min and 30 min before incision compared with administration between 30 min and 60 min. Most other international guidelines still recommend administration of SAP within 60 min before surgical incision; however, administration within the final 30 min is increasingly recommended.

Added value of this study

To our knowledge, this is the first randomised trial examining the effect of different SAP timings on the risk of SSI. Our study showed that early administration of cefuroxime, a commonly used cephalosporin with a short half-life, combined with metronidazole in colorectal surgery, did not significantly lower the risk of SSI compared with late administration before incision.

Implications of all the available evidence

The available evidence so far does not support any narrowing of the 60-min window for the routine administration of a cephalosporin with a short half-life.

the incision time might be too late for optimum SSI prevention.

Based on the available evidence, the joint guidelines from four large American societies concluded that the data are not sufficiently robust to recommend narrowing the 60-min window.[9] This research gap has been identified by the 2016 WHO guidelines, which call for a randomised controlled trial (RCT) to clarify the optimum timing of SAP as a matter of high priority.[19] Such a trial has the potential to have an important impact on present international guidelines for infection control strategies and to be of substantial interest in terms of patient safety and health-care economics. We designed this RCT to test the hypothesis that early administration of cefuroxime would be better than late administration before surgical incision for the prevention of SSI, thereby aiming to confirm the results of the observational study on cefuroxime.[18]

See Online for appendix

For the **protocol** see https://www.ncbi.nlm.nih.gov/pubmed/24885132

Methods

Study design and participants

This phase 3 superiority RCT was done at the University Hospital Basel and the Hospital of Aarau, two tertiary care referral centres in Switzerland. Patients were included if they were 18 years of age or older and underwent inpatient general surgery procedures (specifically gastrointestinal, hernia, endocrine, and breast surgery) as well as orthopaedic trauma and vascular procedures with SAP indicated according to international guidelines.[20] Patients were excluded in case of pre-existing antibiotic therapy within 14 days of surgery and in case of emergency procedures with planned incision within 2 h after registration. A detailed list and explanation of all inclusion and exclusion criteria are provided in the (appendix). The trial, including all respective documents, was approved by the local ethics committees in April, 2012 (Basel: reference number, EK 19/12; Aarau: reference number, EK 2011/037). Insurance coverage of general liability was obtained by both study centres. The study protocol has been reported previously.[21] Written informed consent was obtained from all patients.

Randomisation and masking

Randomisation was stratified by study site and performed centrally on the day of surgery according to a pre-existing computer-generated list, which was provided by a statistician who was not involved in screening patients or assessing outcomes. For the purpose of communication of treatment allocation to the anaesthesia team, the randomisation list was linked with the clinical data system (developed by ProtecData, Boswil, Switzerland). To see the result of randomisation, the members of the anaesthesia team had to log into the clinical data system and press a button with a time stamp. This button was a mandatory item to print their routine preoperative assessment sheet with the treatment plan on the day of surgery. It only appeared if a patient was included in the study. The result was then presented for that specific patient and procedure on-screen and was included in the printed sheet. At no time did the anaesthesiologists or anaesthesia nurses have access to the randomisation list. Patients were screened, their consent obtained, and enrolled by investigators who

were part of the surgical team doing the procedure and who were not involved in assessing outcomes for the purpose of the study. Patients and the outcome assessment team were blinded to group assignment.

Patients were randomly assigned (1:1) to receive SAP in the anaesthesia room, which was located in front of the actual operating room (group A) or in the operating room itself (group B). We estimated that patients in group A would receive SAP early, approximately 30–75 min before the scheduled incision, which reflects the time window with the lowest rates of SSI in the prospective observational cohort study on cefuroxime.[18] We estimated that patients in group B would receive SAP late, approximately 0–30 min before the scheduled incision.

Procedures

SAP was administered by the anaesthesia team to all patients in a standardised manner via single-shot, intravenous infusion of 1·5 g of cefuroxime (GlaxoSmithKline, Verona, Italy) in 100 mL of a 0·9% sodium chloride solution over 2–5 min. It was combined with an intravenous infusion of 500 mg of metronidazole over 2–5 min (B Braun, Rubì, Spain) in colorectal surgery patients who received no bowel preparation with non-absorbable intraluminal antibiotics. In case of a bodyweight equal to or above 80 kg, the doses were doubled (3 g of cefuroxime, 1 g of metronidazole). The exact time in minutes that the infusion started was recorded by the anaesthesiologist or anaesthesia nurse. The same dose of cefuroxime (plus the same dose of metronidazole in colorectal surgery) was given every 4 h after the first administration. In patients with impaired renal function, this redose was adapted according to the creatinine clearance.

The surgical team followed up the patients by routine wound surveillance according to clinical standards including diagnosis and treatment of SSI. The physicians of the ward who were in charge of inpatient care were blinded to the intervention and were responsible for the assessment of SSI for the purpose of this study, which was continuously cross-checked by supervising members of the masked wound surveillance study team. Additionally, the blinded members of the outcome assessment team participated daily in the hospital rounds together with the surgical team and the physicians of the ward, and visited patients directly in case of potential events. For post-discharge follow-up, trained nurses and clinicians at each study site who were masked to group assignment contacted all patients 30 days after surgery by telephone. The past or present occurrence of SSI was assessed by a standardised questionnaire, and the physician who performed post-surgery outpatient clinical controls was identified. Whenever the telephone assessment suggested a possible event, primary care physicians were contacted for detailed information from their charts, and the hospital charts were reviewed as well. After five unsuccessful attempts to contact patients within a period of 4 weeks after the 30-day follow-up, in-hospital charts were screened for readmissions and surgical take-backs. All cases showing evidence of SSI were validated by a board certified infectious diseases specialist at each study site who was blinded to group assignment.

Outcomes

The primary endpoint was the occurrence of any SSI within 30 days after surgery. SSI was defined as incisional (either superficial or deep) or organ or space infection according to the Centers for Disease Control and Prevention (CDC) criteria that were published in 1999.[21] These definitions required a surveillance period of 30 days, which was extended to 1 year in case of implant surgery. Prespecified secondary endpoints included all-cause 30-day mortality and length of hospital stay.

During the conduct of the study, the CDC National Healthcare Safety Network (NHSN) updates called for a change to follow-up duration for several procedures included in this trial. Follow-up was shortened from 12 months to 3 months for implant-based surgery; extended from 1 month to 3 months for breast surgery, herniorrhaphy, and peripheral bypass surgery even when using autologous tissue; and remained unchanged (1 month) for the rest of the procedures in this trial.[22] Therefore, on July 30, 2015, we decided to homogenise the duration of follow-up for all procedures to 1 month because this was prespecified for all procedures in this study, and to abandon the additional follow-up 1 year after surgery in case of implants.

The study was done in compliance with the protocol and according to Good Clinical Practice standards, as well as legal regulations. However, in accordance with the local ethics committees, only serious adverse events were reported to the funder. These included death from any cause, life threatening serious adverse events, serious adverse events that caused a prolongation of the length of hospital stay, serious adverse events that caused a persistent and significant handicap to the patient, and serious adverse events that required an intervention to prevent one or several of the above mentioned. Deaths were additionally reported to the local ethics committees within 7 days of becoming apparent to the study team. SSI were not reported as serious adverse events because they correspond to the endpoint of this study.

Statistical analysis

Our target enrolment was 5000 assessable patients for a 1:1 ratio of patients randomly assigned to have SAP administered early in the anaesthesia room (group A) or late in the operating room (group B). Instead of arbitrarily defining a minimum important reduction of the risk of SSI that would call for a shortening of the recommended time window for the administration of SAP, we derived the assumptions for the sample size calculations from the results of the 2000–01 observational study at the University

Hospital Basel.[18] We assumed that administration of SAP early in the anaesthesia room would result in a 33% relative reduction of SSI risk and that the SSI risk with SAP administration in the operating room would be 5%. Together with a power of 80% and a two-sided type I error of 5%, these assumptions resulted in two groups of 2500 patients each.

The main analyses were by intention-to-treat, which provides a valid estimate of comparing a policy to administer SAP early in the anaesthesia room with a policy to administer SAP late in the operating room. For the binary endpoints 30-day SSI and 30-day all-cause mortality, we present complete case analyses including patients with complete 30-day follow-up. Even though all patients were completely followed up during the hospital stay, not all patients could be contacted after discharge to ascertain SSI and vital status at day 30 (figure 1). To assess robustness of the complete case analyses, we also did all analyses of the 30-day binary outcomes with inverse probability of censoring weights (IPCW).[23,24] IPCW account for the possibility that the likelihood of having obtained follow-up information might vary and might depend on risk factors of SSI and mortality (see appendix for simplified arguments for using IPCW). IPCW were derived from a logistic regression with availability of follow-up information as the outcome, including predictors related to surgery (wound class, surgical division, duration of surgery, and emergency surgery) and to the patient (American Society of Anaesthesiologists score, number of comorbidities, having diabetes, body-mass index [BMI] above 30, being older than 65 years, taking immunosuppressive drugs, and smoking status). We calculated absolute risks of SSI or mortality and used logistic regression to obtain the odds ratios (ORs) and 95% CIs for comparing patients by randomisation groups. Robust SEs were used in the IPCW analyses. For the comparison of length of hospital stay (available for all patients), we used the two-sample Wilcoxon (Mann–Whitney) rank-sum test.

In addition to the intention-to-treat analysis, which assessed the difference between the two policies of administering SAP, we did an as-treated and a per-protocol analysis for the primary outcome of any SSI within 30 days after surgery.[25] As both of these analyses are prone to being biased because of imbalances in prognostic factors, multivariable logistic regression models were used including hospital, wound class, surgical division, duration of surgery, emergency surgery, ASA score, number of comorbidities, having diabetes, BMI above 30 kg/m², being older than 65 years, taking immunosuppressive drugs, and smoking status in addition to the main variable of where SAP was received. These additional analyses were done post hoc and not defined in the study protocol.[21]

We did three prespecified subgroup analyses for age (≥65 years *vs* <65 years), BMI (≥30 kg/m² *vs* <30 kg/m²), and diabetes (with *vs* without). Three subgroup analyses were done post hoc: surgical division (general *vs* trauma *vs* vascular), presence versus absence of immunosuppressive drugs, and wound class (1 *vs* 2 *vs* 3 *vs* 4). For these analyses we included interaction terms between randomisation group and the respective subgroups to obtain Wald-type interaction p values. We provide descriptive statistics for the exact SAP timing by randomisation group. All analyses were done using R and Stata (version 14.1, Stata Corp, College Station, TX, USA).

The clinical trial unit of the University Hospital Basel oversaw the study at both sites and provided continuous central and on-site monitoring. One prespecified interim analysis was done, according to the study protocol, after having recruited and operated on 2500 patients. Decisions for stopping were done using a fully probabilistic approach; they were prespecified in the protocol and strictly followed after the results of the interim analysis became available.[21,26] The obtained predictive probability was 8·36% for a significant result at the end of the study. With this interim result, the study neither fulfilled the criteria for stopping for futility nor for early success and therefore continued to full length. Because of the interim analysis, which also included a criterion for stopping for superiority, a p value of less than 4·5% at the final analysis would have been necessary to claim superiority and preserve an overall type I error of 5%. The trial is registered with ClinicalTrials.gov, number NCT01790529.

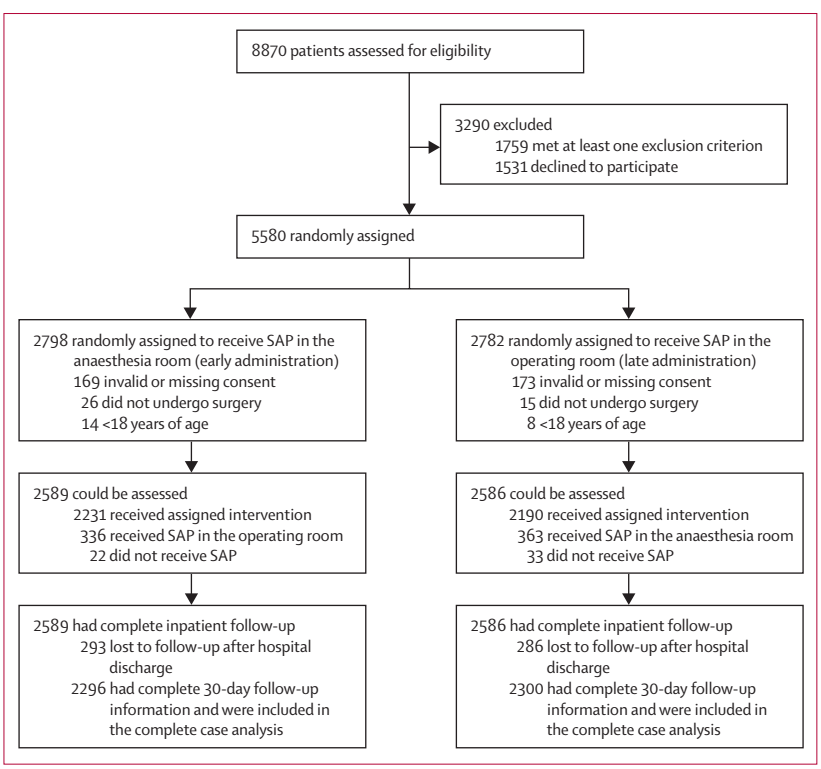

Figure 1: **Trial profile**
SAP=surgical antimicrobial prophylaxis.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	SAP in anaesthesia room, early administration (n=2589)			SAP in operating room, late administration (n=2586)		
	Basel (n=1502)	Aarau (n=1087)	Total (n=2589)	Basel (n=1493)	Aarau (n=1093)	Total (n=2586)
Timing of SAP (min before incision)						
Known	40 (30–55)	43 (32–55)	42 (30–55)	20 (11–30)	14 (9–20)	16 (10–25)
Unknown	12 (1%)	10 (1%)	22 (1%)	17 (1%)	16 (1%)	33 (1%)
Sex						
Men	782 (52%)	630 (58%)	1412 (55%)	777 (52%)	613 (56%)	1390 (54%)
Women	720 (48%)	457 (42%)	1177 (46%)	716 (48%)	480 (44%)	1196 (46%)
Age (years)	60·2 (45·1–73·9)	56·5 (42·0–69·3)	58·4 (43·5–71·9)	60·8 (43·2–72·8)	56·1 (41·1–69·5)	59·0 (42·4–71·5)
ASA score						
1	228 (15%)	227 (21%)	455 (19%)	236 (16%)	241 (22%)	477 (18%)
2	807 (54%)	588 (54%)	1395 (54%)	770 (52%)	569 (52%)	1339 (52%)
3	447 (30%)	265 (24%)	712 (28%)	459 (31%)	277 (25%)	736 (29%)
4	20 (1%)	7 (1%)	27 (1%)	28 (2%)	6 (1%)	34 (1%)
Surgical division						
General	649 (43%)	604 (56%)	1253 (48%)	654 (44%)	604 (55%)	1258 (49%)
Trauma	644 (43%)	358 (33%)	1002 (39%)	633 (42%)	370 (34%)	1003 (39%)
Vascular	209 (14%)	125 (12%)	334 (13%)	206 (14%)	119 (11%)	325 (13%)
Wound class						
1	1306 (87%)	739 (68%)	2045 (79%)	1294 (87%)	740 (68%)	2034 (79%)
2	135 (9%)	266 (25%)	401 (16%)	137 (9%)	258 (24%)	395 (15%)
3	43 (3%)	73 (7%)	116 (5%)	43 (3%)	77 (7%)	120 (5%)
4	18 (1%)	9 (1%)	27 (1%)	19 (1%)	18 (2%)	37 (1%)
Diabetes						
No	1367 (91%)	970 (89%)	2337 (90%)	1478 (91%)	996 (91%)	2358 (91%)
NIDD	74 (5%)	84 (8%)	158 (6%)	72 (5%)	64 (6%)	136 (5%)
IDD	61 (4%)	33 (3%)	94 (4%)	59 (4%)	33 (3%)	92 (4%)
Immunosuppressive drugs						
No	1488 (99%)	1070 (98%)	2558 (99%)	1478 (99%)	1079 (99%)	2557 (99%)
Yes	14 (1%)	17 (2%)	31 (1%)	15 (1%)	14 (1%)	29 (1%)
BMI, kg/m²	25·3 (22·6–29·1)	26·3 (23·7–30·7)	25·7 (23·0–29·6)	25·4 (22·5–29·3%)	26·3 (23·2–30·1)	25·8 (22·8–29·6)
Unknown	32 (2%)	1 (<1%)	33 (1%)	36 (2%)	0	36 (1%)
Preoperative albumin, g/L	37 (34–40)	38·6 (24·7–41·6)	37·9 (34–40)	37 (34–40)	38·4 (35·8–40·6)	37 (34·4–40)
Unknown	422 (28%)	887 (82%)	1309 (51%)	435 (29%)	880 (81%)	1315 (51%)
Preoperative eGFR, mL/min per 1·73 m²	87·8 (70·4–101·6)	79·2 (63·8–96·4)	85·8 (67·8–100·2)	87·4 (70·6–101·1)	82·9 (61·9–98·4)	85·9 (67·5–100·1)
Unknown	416 (28%)	557 (51%)	979 (38%)	428 (29%)	536 (49%)	964 (37%)
Emergency procedure						
Yes	159 (11%)	312 (29%)	471 (18%)	145 (10%)	302 (28%)	447 (17%)
No	1343 (89%)	775 (71%)	2118 (82%)	1348 (90%)	791 (72%)	2139 (83%)
Duration of surgery	85 (57–125)	95 (61–155)	90 (60–135)	85 (55–121)	95 (62–151)	89 (60–135)
Intraoperative redosing						
Yes	30 (2%)	142 (13%)	172 (7%)	27 (2%)	119 (11%)	146 (6%)
No	1472 (98%)	945 (87%)	2417 (93%)	1466 (98%)	974 (89%)	2440 (94%)

Data are median (IQR) or n (%). Percentages have been rounded to nearest whole percentage and may not total to 100%. SAP=surgical antimicrobial prophylaxis. ASA=American Society of Anesthesiologists. NIDD=non-insulin-dependent diabetes. IDD=insulin-dependent diabetes. BMI=body-mass index. eGFR=estimated glomerular filtration rate. Emergency procedure=non-elective procedures with planned incision >2 h after registration.

Table 1: **Baseline characteristics of the intention-to-treat population**

	SAP in anaesthesia room, early administration (n=2296)*	SAP in operating room, late administration (n=2300)*	Odds ratio (95% CI)	p value†
Primary outcome				
Surgical site infection	113 (5%)	121 (5%)	0·93 (0·72–1·21)	0·601
Superficial incisional infection	48 (2%)	55 (2%)	0·87 (0·59–1·29)	0·491
Deep incisional infection	23 (1%)	20 (1%)	1·15 (0·63–2·11)	0·642
Organ space infection	42 (2%)	46 (2%)	0·91 (0·60–1·39)	0·673
Secondary outcomes				
All-cause 30-day mortality	29 (1%)	24 (1%)	1·21 (0·70–2·09)	0·485
Median length of hospital stay, days	5·1 (3–9)	5·0 (3–10)	NA	0·375

Data are n (%) or median (IQR). For the secondary outcome all-cause 30 day mortality, the complete case set numbers were 2301 in the early and 2306 in the late group. For the secondary outcome median length of hospital stay, the complete case set numbers are equal to the total study population (ie, 2589 for the early group and 2586 for the late group). SAP=surgical antimicrobial prophylaxis. NA=not applicable. *These numbers represent the complete case set (ie, the numbers of cases with complete 30-day follow-up). †p values for binary outcomes are Wald p values from logistic regression and for length of stay from a Wilcoxon (Mann–Whitney) rank-sum test.

***Table 2*: Effect of early *vs* late administration of surgical antimicrobial prophylaxis on primary and secondary outcomes in the intention-to-treat analysis**

Results

Between Feb 21, 2013, and Aug 3, 2015, 8870 patients were assessed for eligibility, 3290 of whom were excluded (1759 because of the presence of at least one exclusion criterion, and 1531 declined to participate; figure 1). The remaining 5580 patients were randomly assigned to receive SAP early in the anaesthesia room (2798 patients) or late in the operating room (2782 patients.) Of those 5580 randomly assigned patients, 41 (1%) did not undergo surgery, 22 (<1%) were younger than 18 years, and 342 (6%) had an invalid or missing informed consent form. These patients were excluded post-randomisation and the study continued to a total accrual of 5175 patients, 2995 in Basel and 2180 in Aarau, for the primary intention-to-treat analysis (2589 in the early and 2586 in the late group). A small number of patients (n=64) that received SAP before incision and were later categorised as having wound class 4 were included in the intention-to-treat analysis.

In the group that was randomly assigned to receive SAP in the anaesthesia room (early group), 336 (13%) received SAP in the operating room (late group). In the group that was assigned to receive SAP in the operating room, 363 (14%) patients received SAP in the anaesthesia room. Median administration time in the early group was 42 min (IQR 30–55) before incision and in the late group was 16 min (10–25) before incision. In the early group, 16 patients were given SAP after incision and 22 patients did not receive the study drug. In the late group, 21 patients were given SAP after incision and 33 did not receive the study drug.

All 5175 patients were followed up until discharge, and 4596 (89%) of these were successfully followed up after 30 days. A similar number of participants in each group were lost to 30-day outpatient follow-up: 293 (11%) in the early group and 286 (11%) in the late group. Distributions of patient and procedure characteristics for the two groups were similar (table 1).

The overall SSI rate was 5·1% (234 of 4596) in patients with a complete 30-day follow-up, with 113 (4·9%) of 2296 SSI occurring in the early group and 121 (5·3%) of 2300 SSI in the late group (table 2). About half of all SSI (120 of 234) were registered during the hospital stay and half (114 of 234) after discharge, with no significant difference between the two groups.

Early administration of SAP did not significantly reduce the risk of SSI compared with late administration (odds ratio [OR] 0·93, 95% CI 0·72–1·21, p=0·601). These results were almost identical in the IPCW analysis (0·93, 0·72–1·21, p=0·598; appendix). When repeating the intention-to-treat analysis after exclusion of the 37 patients who had SAP administered after incision and those 55 received who no SAP, the results remained virtually unchanged (0·93, 0·71–1·21, p=0·573). Similarly, after exclusion of all patients who had an upgrade of their wound class to category 4 during surgery, the results remained almost identical (0·94, 0·72–1·23, p=0·667).

The as-treated analysis included 2567 patients who received SAP in the anaesthesia room and 2553 who received SAP in the operating room (OR 0·78, 95% CI 0·59–1·04, p=0·093). The per-protocol analysis included 2231 patients who received SAP in the anaesthesia room and 2190 who received SAP in the operating room (0·86, 0·64–1·17, p=0·335). Both of these post-hoc analyses showed a more pronounced reduction of the odds of SSI, but did not provide significant evidence favouring early over late administration of SAP. When excluding the 64 patients who were categorised as having wound class 4, the 37 patients who had SAP administered after incision, and the 55 who received no SAP, the as-treated analysis of 4469 patients revealed an OR of 0·80 (95% CI 0·60–1·07, p=0·135).

The rates of SSI did not differ between the two groups for all three types of SSI (table 2). Several prespecified and post-hoc subgroups were examined and provided no evidence for a modification of the effect of early versus late administration of SAP (figure 2).

Because culture or non-culture-based testing is not mandatory according to the CDC definitions of SSI, only 73 (61%) of 120 patients with in-hospital diagnosis of SSI had pathogens isolated. Table 3 shows the spectrum of pathogens isolated from patients with SSI. Importantly, the presence of multidrug-resistant pathogens in patients with SSI was extremely low at both study sites.

There were no significant differences between randomisation groups for the secondary endpoints all-cause 30-day mortality, and median length of hospital stay (table 2).

Discussion

To our knowledge, this is the first randomised trial examining the effect of different SAP timings on the

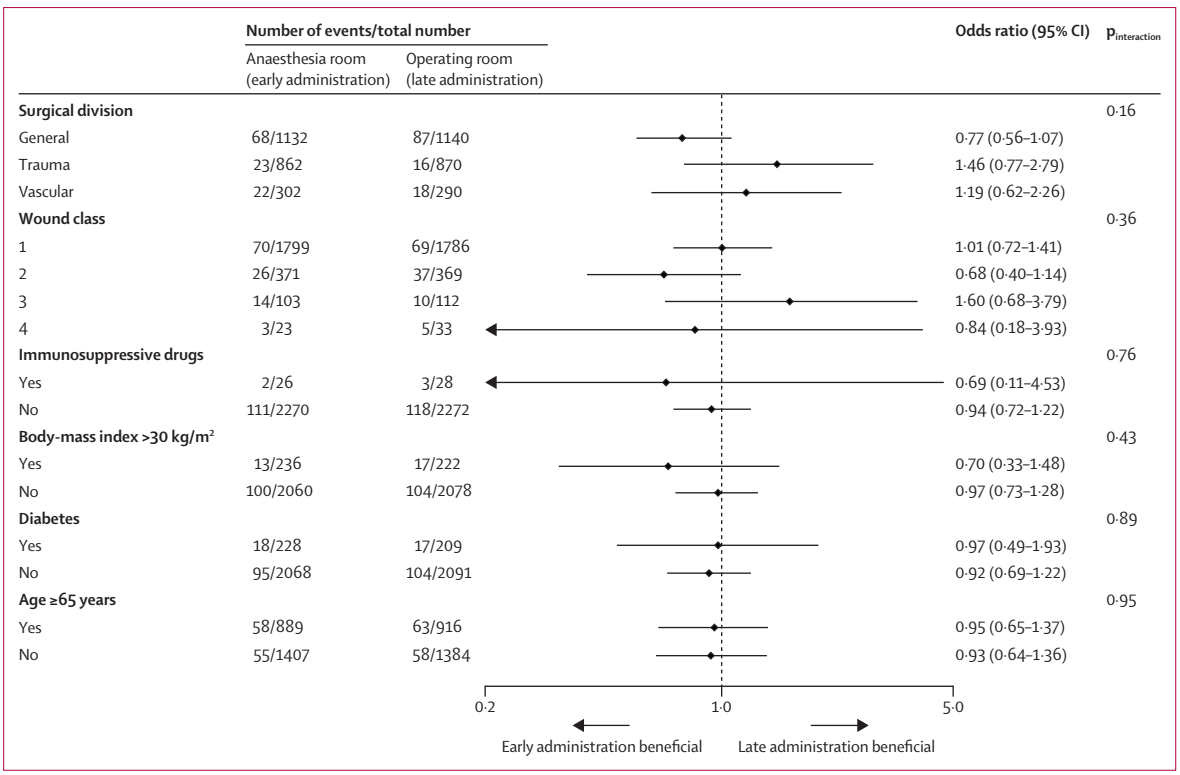

Figure 2: **Subgroup analyses of the effect of early *vs* late surgical antimicrobial prophylaxis administration on surgical site infection**
The analyses were done according to intention to treat. Three subgroup analyses were prespecified: age (≥65 years *vs* <65 years), body-mass index (≥30 kg/m² *vs* <30 kg/m²) and diabetes (with *vs* without). Three subgroup analyses were done post hoc: surgical division (general *vs* trauma *vs* vascular), presence versus absence of immunosuppressive drugs, and wound class (1 *vs* 2 *vs* 3 *vs* 4). Estimates for the relative effect of early *vs* late administration of antibiotic prophylaxis on the risk of surgical site infection in each subgroup are presented as odds ratios with 95% CIs. Interaction terms were included between randomisation group and the respective subgroups to obtain interaction p values.

risk of SSI. The present results showed that early administration of cefuroxime, a commonly used cephalosporin with a short half-life, plus metronidazole in colorectal surgery did not significantly lower the risk of SSI compared with late administration before incision. The secondary endpoints all-cause 30-day mortality and length of hospital stay also remained unaffected. The study was not underpowered as the observed SSI rate of 5·1% (in 234 of 4596 patients) was in agreement with our assumptions for the sample size calculation.[18]

Our study addressed two opposing trends in SAP timing recommendations that aim to refine the broad recommendation of administering SAP with a short half-life and infusion time within 60 min before surgery.[5,8-10,19] On the one hand, several guidelines favour late administration of SAP close to the incision time.[15,16,27] The largest observational study so far, examining the association between antibiotic timing and SSI risk showed a trend towards lowest risk of SSI when SAP with cephalosporins and other antibiotics with short infusion times were given within 30 min before incision.[13] A second study showed a decreasing rate of infections after total hip arthroplasty in patients who received antibiotics within 30 min before incision, and a third study showed that the lowest rate of infections occurred after various procedures when the antibiotics were given 10–20 min before incision.[12,14]

On the other hand, SAP timing should ensure that tissue drug levels exceed the minimum inhibitory concentration for organisms likely to be present at the surgical site throughout the operation. The hypothesis that administration of antibiotics with a short half-life immediately before incision might be too late for optimum SSI prevention was supported by a prospective pharmacokinetic study that used in-vivo microdialysis to measure continuous tissue levels of cefazolin.[28] The authors concluded that cefazolin should be administered at least 60 min before skin incision to guarantee for optimum tissue concentration at the beginning of surgery. Vast interindividual differences were observed for the time required to reach maximum interstitial concentrations.

Additionally, some observational studies suggested that administration of SAP shortly before incision might be too late for optimum SSI prevention. In a combined analysis of data from two small RCTs of single-dose piperacillin versus multidose cefoxitin, the lowest rate of infection (13%) was seen when the drug was given

	SAP in anaesthesia room, early administration (n=2296)		SAP in operating room, late administration) (n=2300)	
	Basel (n=1217)	Aarau (n=1079)	Basel (n=1216)	Aarau (n=1084)
Surgical site infection	62 (5·1%)	51 (4·7%)	62 (5·1%)	59 (5·4%)
Identification of pathogen				
Yes	13	19	17	24
No	49	32	45	35
Pathogens				
Escherichia coli	4	7	6	8
Enterococcus spp	3	5	4	7
Coagulase negative staphylococci	5	1	4	3
Streptococcus viridans	2	1	2	5
Staphylococcus aureus	1	3	3	2
Other Enterobacteriaceae	1	2	1	4
Klebsiella spp	1	0	0	5
Pseudomonas aeruginosa	2	1	1	2
Other anaerobic bacteria	1	2	1	0
Enterobacter spp	0	2	0	1
Bacterioides spp	0	2	0	1
Candida albicans	0	2	0	1
Serratia spp	0	0	0	2
Pseudomonas, non-*aeruginosa*	2	0	0	0
Clostridium spp	0	2	0	0
Candida spp	1	1	0	0
Bacillus spp	0	1	0	0
Other Gram-positive bacteria	1	0	0	0
Proteus spp	0	1	0	0
Multidrug-resistant pathogens				
ESBL	1	0	1	2
Others	0	1	0	2
MRSA	0	1	0	0

There were 113 (5%) of 2296 SSI for SAP administered in anaesthesia room and 121 (5%) of 2300 SSI for SAP administered in operating room. SAP=Surgical antimicrobial prophylaxis. ESBL=extended spectrum β-lactamase. MRSA=meticillin-resistant staphylococcus aureus.

Table 3: **Spectrum of pathogens in surgical-site infections (SSI) by study site**

between 16 and 60 min before surgery, compared with 21% when given within 15 min before surgery.[17] The authors listed inability to complete preoperative antibiotic infusion before the beginning of the operation as the most plausible reason for the high infection rate associated with the late administration of antibiotics.

The largest prospective observational cohort study on cefuroxime analysed the incidence of SSI by the timing of SAP in a series of 3836 consecutive general surgical procedures.[18] In multivariable logistic regression analyses, the odds of SSI were almost doubled when SAP was administered less than 30 min compared with the reference interval of 30–59 min before incision (adjusted OR 1·95, 95% CI 1·4–2·8, p<0·001). Although SAP was given to most patients between 0 min and 44 min and before incision, the lowest rate of SSI was recorded when the antibiotics were administered between 30 min and 74 min before surgery. Based on this study, Swiss guidelines recommend the administration of SAP with cefuroxime (combined with metronidazole in colorectal surgery) between 30 min and 74 min before skin incision.[29] However, corroboration of these findings ideally in a RCT was encouraged by the editorial accompanying the study.[30] Our study did not confirm that a policy to administer SAP early in the anaesthesia room would significantly reduce the risk of SSI compared with a policy to administer SAP late in the operating room, and we conclude that the statistical analysis could not reliably adjust for all inherent biases of that previous observational study.

The results from the intention-to-treat analysis with an OR of 0·93 and a 95% CI of 0·72–1·21 for early versus late administration of SAP before surgery do not support any narrowing of the 60-min window. This is clinically relevant, because the timing of SAP is widely used as a quality criterion in surgical infection prevention projects.[5,10] Many centres have problems initiating the infusion within 60 min before surgery, and narrowing this window, as recommended by several guidelines, would make this target even more difficult.[15,16,29] Timing difficulties even occurred in the controlled setting of this RCT, with 699 (14%) of 5175 patients not receiving the assigned intervention.

Our study is not without limitations; first, the results obtained by the regimen in this study might not be generalisable to other antimicrobial drugs with different pharmacokinetics. The trial was done at two tertiary referral centres in Switzerland, and the results might not be applicable to a differing patient population, such as one with a considerably higher rate of infection or a higher incidence of antimicrobial resistance. The higher dose of SAP administered to patients with a body weight above 80 kg might have changed the pharmacokinetics in this subgroup compared with the dose administered to the rest of the study population. Subgroup analyses suggested a consistent absence of superiority of early versus late administration of SAP across subgroups, which increases the generalisability of our findings. However, given that the underlying SSI rate was only 5·1%, and the study was powered at 80% to detect a large treatment effect (33% relative reduction of SSI risk), we need to acknowledge that the study was only powered to detect large interactions at the subgroup level.

Second, even though patients were not informed about assignments to treatment groups, we cannot exclude that some patients in the early group might have seen the infusion of SAP when given before induction of anaesthesia. Third, the follow-up period of 1 month is insufficient to detect all SSI after implant-based surgery, and outpatient follow-up rate at 1 month was only 88·8% (4596 of 5175 patients). We decided to follow-up patients personally by telephone based on our experience with the previous observational study.[18] We restricted the number of attempts to contact patients to five times within a period of 4 weeks after the 30-day follow-up to ensure that

the patients remembered any potential event. We do not think, however, that missing follow-up data weaken the interpretation of the findings. We followed-up all patients during their hospital stay, and the number of patients lost to outpatient follow-up was equally distributed between the two randomisation groups. We assessed the robustness of the complete case analysis with regard to possible informative loss to follow-up by doing analyses with IPCW in which we obtained very similar results. Fourth, 342 patients were excluded post randomisation because of invalid or missing informed consent. The underlying mechanism for the high rate of missing consent was identified and corrected during the course of the study. In brief, it proved to be difficult to collect all signed consent forms because they were obtained from a large number of units throughout the hospitals. Hence, rather than having the investigators actively send all signed consent forms to the trial office, the practice was changed to have the study nurses of the trial office actively collect all consent forms on a daily basis. However, the number of patients excluded post randomisation was equally distributed between the two groups. Finally, a small number of patients either did not receive SAP at all or had SAP initiated after surgical incision or had a wound class that was upgraded to category 4 during surgery. Exclusion of these patients from the statistical analysis did not change the findings of this study.

In conclusion, early administration of cefuroxime (plus metronidazole in colorectal surgery) did not significantly lower the risk of SSI compared with late administration before incision. Even though the present results do not rule out a beneficial effect of early administration of SAP on the risk of SSI, they do not support changing current recommendations to administer SAP during the 60 min before incision.

Contributors

The study was designed by WPW, RR, MZ, and WRM. WPW, EM, MB, HH, SDS, MKa, TD, MuS, LI, RXSDS, JZ, RR, HM, CK, PM, AKL, MKr, LG, DO, UvH, EB-L, JL, AFW, CAF, and WRM collected the data. RS did central data review and preparation of the data for statistical analysis. RS and MZ did all statistical analyses. WPW, EM, MB, HH, SDS, MKa, TD, MvS, LI, RXSDS, JZ, RR, HM, CK, PM, AKL, MKr, LG, DO, UvH, EB-L, JL, AFW, CAF, RS, MZ, and WRM contributed to the final draft of the manuscript and vouch for the accuracy and completeness of the data.

Declaration of interests

WPW reports grants from the Swiss National Science Foundation, Hospital of Aarau, University of Basel, Gottfried und Julia Bangerter-Rhyner Foundation, Hippocrate Foundation, and Nora van Meeuwen-Häfliger Foundation, during the conduct of the study; WPW received a research grant from Takeda Pharmaceuticals International for another randomised controlled trial not related to this work and has consulted for Genomic Health in the past. EM, MB, HH, SDS, MKa, TD, MvS, LI, RXSDS, JZ, HM, CK, PM, RS, AKL, MKr, LG, DO, EB-L, JL, CAF, and WRM report grants from the Swiss National Science Foundation, Hospital of Aarau, University of Basel, Gottfried und Julia Bangerter-Rhyner Foundation, Hippocrate Foundation, and Nora van Meeuwen-Häfliger Foundation, during the conduct of the study. MZ reports grants from Swiss National Science Foundation, during the conduct of the study; and grants from Swiss National Science Foundation, AstraZeneca, Aptalis Pharma, Dr Falk Pharma, Germany, GlaxoSmithKline, Nestlé, Switzerland, Receptos, Regeneron; and personal fees from Board member of Bern Cancer League and World Cancer Research Fund International, outside the submitted work. RR reports grants from the Swiss National Science Foundation, Hospital of Aarau, University of Basel, Gottfried und Julia Bangerter-Rhyner Foundation, Hippocrate Foundation, and Nora van Meeuwen-Häfliger Foundation, during the conduct of the study, outside the submitted work; and is an employee of F Hoffmann-La Roche since May 1, 2014. The present study has no connection to RR's employment by the company, and RR continues to be affiliated with the University of Basel. AFW reports grants from the Swiss National Science Foundation, Commission for Technology and Innovation, and University of Basel, during the conduct of the study.

Acknowledgments

No commercial support was provided for this study. The study was primarily funded by the Swiss National Science Foundation. Additional funding was received from the Hospital of Aarau, the University of Basel, the Gottfried und Julia Bangerter-Rhyner Foundation, the Hippocrate Foundation, and the Nora van Meeuwen-Häfliger Foundation. We thank Julia Gutzwiller, Aline Koller, Jennifer Luell, Kawa Yousef, Evi Hoene, Franziska Maeder, and Constanze Spelters for their assistance in data collection; Yannick Franc for assisting in conducting the interim analysis; and Cornel Kaufmann for programming the software for data capturing and management.

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