



# Addition of benzylpenicillin to antibiotic prophylaxis reduces deep sternal wound infection after cardiac surgery

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## SUMMARY

**Objectives:** In Sweden, cloxacillin is recommended as the sole antibiotic prophylaxis for prevention of surgical site infections after cardiac surgery. *Cutibacterium acnes*, formerly *Propionibacterium acnes*, has been shown to be present in the surgical wound. Formerly an overlooked pathogen, there are increasing reports that *C acnes* can cause surgical site infections, including sternal wound infections. Cloxacillin may not be optimal for prevention of *C acnes* infection, therefore benzylpenicillin was added to our routine intra-operative prophylaxis in 2015. The aim of this study was to investigate the effect of benzylpenicillin on incidence of sternal wound infection.

**Methods:** We included 3920 consecutive patients that underwent cardiac surgery via median sternotomy at our centre from 2009 thru 2018. All patients were followed up two months postoperatively. The rate of sternal wound infection before and after 2015 were compared. Logistic multivariable analysis was used to adjust for potential confounders.

**Results:** The mean incidence of sternal wound infection that required surgical revision decreased from 4.7% to 1.7% after addition of benzylpenicillin ( $p < 0.001$ ). Significant decrease was seen in sternal wound infections caused by Coagulase negative staphylococci, either alone ( $p < 0.001$ ) or concomitant with *C acnes* ( $p = 0.008$ ). Addition of benzylpenicillin remained independently associated with the reduction of sternal wound infections in the multivariable analysis (OR=0.36 CI=0.23–0.56,  $p < 0.001$ ).

**Conclusions:** Addition of benzylpenicillin was associated with a reduction in surgically treated infections and might be effective against infection caused by CoNS with and without co-infection by *C acnes*, although the exact underlying mechanism is unknown.

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## Introduction

Surgical site infection (SSI) is a serious post-operative complication and unfortunately, a common healthcare

associated infection. In cardiac surgery, the incidence of SSI in the sternal wound is 3.5–9.7% [1–4]. Common risk factors for SSI in cardiac surgery include cardiovascular disease, diabetes mellitus, smoking, body mass index (BMI)  $\geq 30$  and use of corticosteroids [1,5].

The most common pathogens that cause sternal wound infection (SWI) are *Staphylococcus aureus* and Coagulase

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negative staphylococci (CoNS), followed by other gram-positive bacteria and gram-negative rods [5]. *Cutibacterium acnes*, formerly *Propionibacterium acnes*, is a gram-positive anaerobe with low virulence and slow growth. It resides in the sebaceous glands of the chest and is actually present in the surgical wound during surgery [6,7]. Historically considered a non-pathogenic part of the normal skin flora, *C. acnes* has in recent years proven to be a significant pathogen in various surgical settings [8–10]. *C. acnes* produces biofilm that enhances virulence and might provide favourable conditions for other species as well. As a notable property it appears to be resistant to preoperative skin disinfection with chlorhexidine in ethanol [11,12]. It has been detected in a considerable number of SWI cases [13,14] although it may be easily overlooked since it requires special culturing conditions [14]. In a previous study we found *C. acnes* to be a relatively frequent etiological agent in deep sternal wound infections (DSWI), however it was rarely found in superficial SWIs [13,15].

Intravenous antibiotic prophylaxis is routinely practised in cardiac surgery to reduce the risk of SSI. Internationally, cephalosporins are most frequently recommended. Addition of vancomycin has been proposed although there are concerns that routine use may lead to increased selection of resistant bacterial strains, and because of its potential nephrotoxicity [16,17]. In Sweden, penicillinase-resistant penicillins (e.g. cloxacillin) are most commonly used [18].

Studies in orthopaedic surgery have indicated that benzylpenicillin might be the most effective drug against *C. acnes* [10,19]. The minimally inhibitory concentrations (MIC) for benzylpenicillin (MIC<sub>50</sub> 0.008 mg/L) was 15.6-fold lower when compared to oxacillin (MIC<sub>50</sub> 0.125 mg/L), which is an isoxazolyl penicillin closely related to cloxacillin [10]. We hypothesised that more effective prevention of *C. acnes* could reduce the incidence of DSWI. Therefore, a single preoperative dose of benzylpenicillin was added to the prophylaxis at our centre as from January 2015.

The aim of the study was to investigate the total incidence of postoperative infections before and after addition of benzylpenicillin to the perioperative prophylaxis. Secondary measures included incidence of infections caused by *C. acnes* and of infections that required surgical revision.

## Patients and methods

### Patients

This study was approved by the Swedish Ethical Review Authority, region of Uppsala, diary number 2019-01043. No informed consent was obtained due to the retrospective nature of the study. The study population consisted of 4324 consecutive patients who underwent cardiac surgery via median sternotomy at the Department of Cardiothoracic and Vascular Surgery, Örebro University Hospital, Sweden from January 1st, 2009 until December 31st, 2018. The centre is the sole provider of cardiac surgery in this geographical region. All patients in need of surgical revision were referred back to our centre. Pre-, intra- and postoperative data, including infectious complications was obtained from our local quality registry. In January 2009 we introduced a systematic post-operative follow-up of all cardiac surgery patients and the data was added to our local registry. The patients were contacted via telephone at least

two months after discharge, by a dedicated nurse, regarding postoperative symptoms of infection. A standardized questionnaire was used to classify patient reported postoperative symptoms of infection according to a previously described simplified version of the validated ASEPSIS-score [20,21]. In addition to patient reported outcomes, data from medical records was used. For all patients who had undergone surgical revision due to SWI, the type of pathogen and the extent of surgical revision was obtained from medical records.

Transcatheter, and non-sternotomy procedures were not included in the study population. Patients who were lost to the two-month follow-up were excluded. This includes patients who died within two months postoperatively, unless they had developed a verified SWI before death.

### Classification

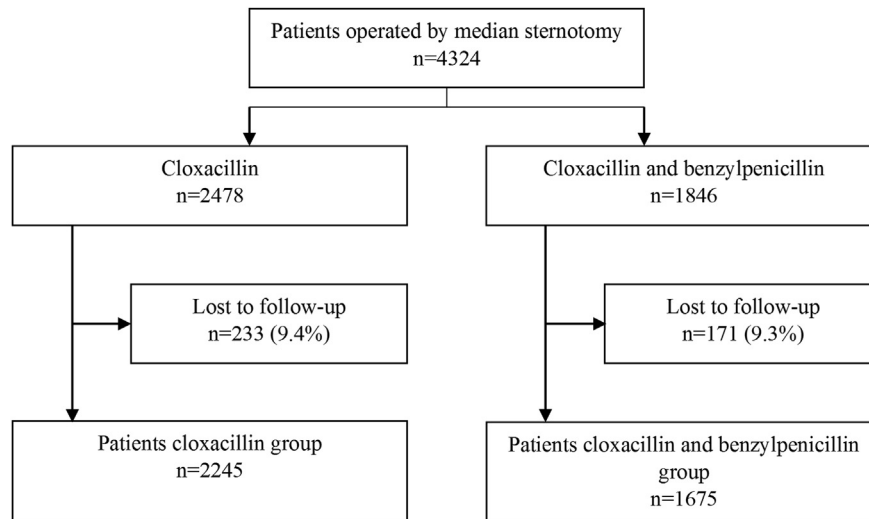
We defined an SWI as any wound complication that had required antibiotic treatment. The need for surgical revision under general anaesthesia was used as a definition of a more severe infection, generally a deep infection. Vacuum assisted closure (VAC)-treatment was used on liberal and similar indications during the entire study period for mediastinitis as well as severe pre-sternal infections. The term “refixation of the sternum” was used to define cases of deep infection where the sternotomy was reopened due to symptoms of infection or mechanical instability. All refixations on these indications were considered as infection in the analyses, irrespective of bacterial findings, as it is difficult to completely rule out infection as the underlying cause in cases of mechanical instability.

### Microbiological findings

Bacterial sampling of surgically revised patients was done on liberal and identical indications during the entire study. All samples were anaerobically cultured. A primary causative agent was determined based on cultured quantities, type of culture and number of cultures where the pathogen was present. In cases of multiple microbial pathogens, the cultures before and during reoperation were examined. The pathogen that had the most abundant growth, and/or was present in the highest number of cultures taken from the deepest layer of the wound, usually mediastinum or sternum, was considered the cause of infection. Where no single pathogen could be determined, the SWI was classified as a co-infection. Bacterial samples on superficial infections, often treated at distant referring hospitals, had been less consistently and systematically collected and were not included in this study.

### Antibiotic prophylaxis and perioperative routines

Patients operated between 2009 – 2014 received perioperative monotherapy of cloxacillin. Two grams of cloxacillin were administered intravenously starting 25 minutes before and terminated 5 minutes before the sternal skin incision. Another dose of two grams was administered two hours after the initial dose and repeated every sixth hour for lengthy operations. A final intraoperative dose was given at the time of sternal closure, but at the earliest two hours after the previous dose. Postoperatively, two grams of cloxacillin were administered every eight hours until the next morning, continuing the



**Figure 1.** Exclusion process of patients identified in the local quality registry at the Department of Cardiothoracic and Vascular Surgery, Örebro University Hospital, Sweden.

**Table I**

Baseline characteristics and operative factors in patients in cloxacillin only and cloxacillin with addition of benzylpenicillin groups

	Cloxacillin (n = 2245)	Cloxacillin and benzylpenicillin (n = 1675)	P value
<b>Risk factors</b>			
Age, y	68 (10)	68 (10)	0.66
Sex, male n (%)	1628 (73)	1250 (75)	0.14
Weight, kg	82 (15)	84 (16)	0.003
Height, cm	173 (9)	173 (9)	0.71
BMI, kg/m <sup>2</sup>	27 (4)	28 (5)	0.36
P-creatinine, μmol/L	92 (55)	87 (45)	<0.001
Additive EuroSCORE	5 (3)	5 (3)	0.46
Smoking	(n=2144)	(n=1622)	0.005
Never smoked n (%)	958 (45)	799 (49)	
Smoker n (%) <sup>a</sup>	1186 (55)	823 (51)	
Diabetes mellitus n (%)	489 (22)	439 (26)	0.001
COPD n (%)	135 (6)	110 (7)	0.50
NYHA class	(n=2140)	(n=1653)	<0.001
I n (%)	183 (9)	120 (7)	
II n (%)	694 (32)	633 (38)	
III n (%)	1117 (52)	834 (51)	
IV n (%)	146 (7)	66 (4)	
Steroids/immunosuppressives n (%)	109 (5)	58 (3)	0.032
<b>Operative factors</b>			
Local Gentamicin n (%)	1161 (52)	1114 (67)	<0.001
Operation time, min	228 (84)	247 (81)	<0.001
ECC-time, min	112 (61)	127 (60)	<0.001
Aortic cross-clamp, min	77 (42)	88 (40)	<0.001
CABG n (%)	1411 (51)	1009 (60)	0.096
Reexploration for bleeding n (%)	109 (5)	42 (3)	<0.001
Single IMA n (%)	974 (43)	573 (34)	<0.001
Bilateral IMA n (%)	3 (0.1)	3 (0.2)	0.72

Figures shown as n (%) or mean (SD). BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ECC = extracorporeal circulation; IMA = internal mammary artery; NYHA = New York Heart Association Functional Classification.

<sup>a</sup> Smoker includes previous smoking.

**Table II**  
Post-operative sternal wound infections and mortality

Total (n=3920)	Cloxacillin (n=2245)	Cloxacillin and benzylpenicillin (n=1675)		
Post-operative SWI	n (%)	n (%)	RR (95%CI)	P value
All infections	174 (7.8)	84 (5.0)	0.65 (0.50–0.83)	0.001
Antibiotic treatment only	69 (3.1)	55 (3.3)	1.07 (0.75–1.51)	0.71
Revision, general anaesthesia <sup>a</sup>	105 (4.7)	29 (1.7)	0.37 (0.25–0.56)	<0.001
Refixation <sup>b</sup>	73 (3.3)	20 (1.2)	0.37 (0.23–0.60)	<0.001
VAC-treatment <sup>b</sup>	92 (4.1)	26 (1.6)	0.38 (0.25–0.58)	<0.001
<b>Post-operative mortality</b>				
Mortality within two months	5 (0.2)	0 (0.0)		0.053

<sup>a</sup> Revision due to deep sternal wound infection, not due to bleeding or other complications.

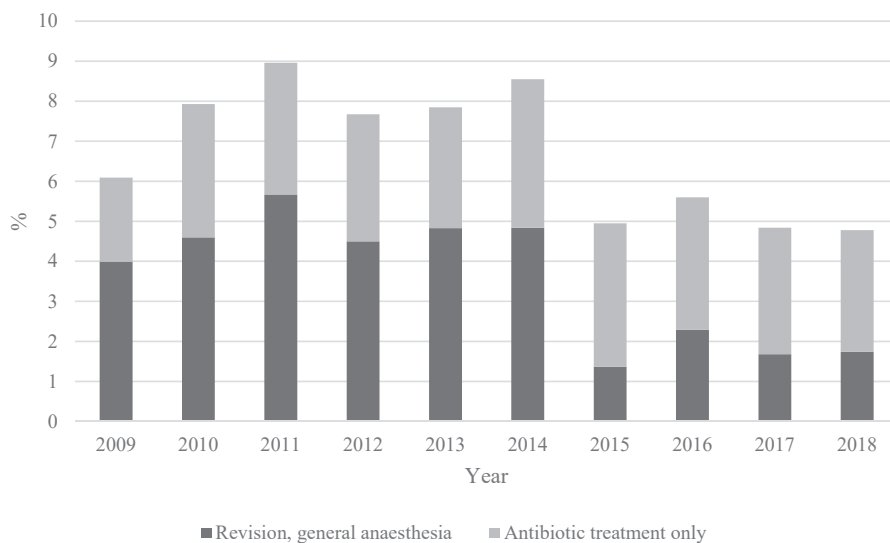
<sup>b</sup> Refixation after revision for wound infection and VAC-treatment in patients who were revised in general anaesthesia. RR = relative risk; SWI = sternal wound infection; VAC = vacuum assisted closure.

prophylaxis for a total length of at least 24 hours. Patients operated 2015–2018 received the same regimen, but with addition of a three-gram single dose of benzylpenicillin, together with the preoperative dose of cloxacillin. Local collagen gentamicin (Collatamp-G®, SERB SAS, Paris, France) between the sternal halves was used throughout the whole study period [21]. Our local guidelines recommended use in patients with diabetes, obesity and immunosuppression, however the final decision was at the discretion of each surgeon [21]. Patients with allergy to beta-lactam antibiotics received clindamycin 600mg; preoperatively, repeated after 4 hours of surgery, then every eight hour for a total of 24 hours.

Until 2013, the sterile draping routine included a transparent plastic adhesive drape covering the chest, after which it was no longer applied. In all other aspects, the same protocol was followed regarding preoperative preparations, and peri- and postoperative management in both groups. The senior surgeons were the same individuals during the entire study period.

### Statistical analysis

Sums, percentages, means and standard deviations were calculated using conventional arithmetic. Chi square test was used for categorical variables and Mann-Whitney U test was used for continuous variables. Relative risk was calculated and disclosed with a 95% confidence interval. Binary logistic regression was performed to adjust for potential confounding factors. Variables included in the regression analysis were known risk factors; BMI, female sex, smoking, diabetes mellitus, chronic obstructive pulmonary disease (COPD), New York Health Association (NYHA) class  $\geq 3$ , operation time and use of a single internal mammary artery. Also, treatment with local gentamicin, that differed between the groups was included. Hosmer-Lemeshow test was used to test the goodness of fit for the final model. A p-value of less than 0.05 was considered significant. Tables were constructed in Microsoft® Excel® version 1902. Statistical analyses were conducted in IBM® SPSS® Statistics version 25.



**Figure 2.** Incidence of post-operative sternal wound infection by year.

**Table III**  
Multivariable logistic regression analysis model of surgically revised SWI

Risk factors and interventions	Unadjusted analysis (n=3920)			Adjusted analysis (n=3664)		
	OR	95% CI	P value	OR	95% CI	P value
Addition of benzylpenicillin	0.36	0.24–0.54	<0.001	0.36	0.23–0.56	<0.001
Local gentamicin	0.74	0.52–1.04	0.083	0.46	0.30–0.70	<0.001
Sex, female	1.10	0.75–1.61	0.64	1.50	0.98–2.30	0.060
Smoking <sup>a</sup>	1.57	1.10–2.24	0.012	1.49	0.99–2.23	0.054
Diabetes mellitus	2.49	1.75–3.53	<0.001	2.24	1.49–3.36	<0.001
COPD	1.80	1.02–3.17	0.044	1.77	0.96–3.24	0.067
NYHA class $\geq$ III <sup>b</sup>	1.53	1.06–2.19	0.022	1.23	0.82–1.84	0.31
Single IMA	1.94	1.37–2.74	<0.001	1.92	1.30–2.84	0.001
BMI 18.5 – < 25						
BMI < 18.5	2.08	0.27–16.12	0.49	1.68	0.20–14.26	0.64
BMI 25 – < 30	1.79	1.07–3.01	0.028	2.01	1.14–3.53	0.015
BMI $\geq$ 30	2.38	1.39–4.06	0.001	2.57	1.41–4.71	0.002
Operation time < 3 h						
Operation time 3–4 h	0.72	0.45–1.16	0.18	0.80	0.48–1.34	0.39
Operation time 4–5 h	1.12	0.68–1.84	0.66	1.32	0.76–2.29	0.32
Operation time > 5 h	1.53	0.93–2.51	0.094	2.15	1.24–3.72	0.006

BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; IMA = internal mammary artery; NYHA = New York Heart Association Functional Classification; OR = odds ratio.

<sup>a</sup> Smoking includes previous smoking, n=3766 due to missing data.

<sup>b</sup> n=3793 due to missing data.

## Results

### Patients

During the study period, 4324 patients underwent cardiac surgery via median sternotomy. Of these, 404 (9.3%) were lost to follow-up and excluded from this study, Figure 1. Eighty-eight (3.6%) patients who received cloxacillin only and 61 (3.3%) patients who received addition of benzylpenicillin died before the two-month follow-up (p=0.66). Patients who had a documented SWI within two months of the surgery but subsequently died were included in the study. In total, 3920 patients were analysed. Baseline characteristics and surgical factors are shown in Table I. Demographics of the excluded patients are shown in the Appendix, Table A1.

### Sternal wound infections

The mean annual incidence of all treated infections decreased from 7.8% to 5.0% (p = 0.001) after addition of benzylpenicillin in 2015, Table II, Figure 2. The decrease was isolated to infections that required surgical revision in general anaesthesia (annual mean 4.7% vs 1.7%, p<0.001). The rate of DSWI that required sternal refixation declined from 3.3% to 1.2% (p<0.001).

After adjusting for differences in baseline data, the addition of benzylpenicillin was independently associated with a highly significant reduction in the incidence of surgically revised SWI (adjusted odds ratio (OR)=0.36, 95% confidence interval (CI)=0.23–0.56, p <0.001), Table III. The Hosmer-Lemeshow test was non-significant (p=0.37) which is expected for a well-fitting multivariable model.

**Table IV**  
Frequency of surgically revised SWI by pathogen before and after addition of benzylpenicillin

Bacterial agent	Cloxacillin (n=2245)		Cloxacillin and benzylpenicillin (n=1675)		RR (95% CI)	P value
	n	%	n	%		
CoNS	35	1.6	2	0.1	0.08 (0.02–0.32)	<0.001
CoNS and <i>C acnes</i>	23	1.0	5	0.3	0.29 (0.11–0.77)	0.008
<i>S aureus</i>	17	0.8	10	0.6	0.79 (0.36–1.72)	0.55
<i>C acnes</i>	14	0.6	5	0.3	0.48 (0.17–1.33)	0.15
Gram-negative bacteria	6	0.3	3	0.2	0.67 (0.17–2.68)	0.57
Other	4	0.2	2	0.2	0.67 (0.12–3.65)	0.64
Negative or unknown culture	6	0.3	2	0.2	0.45 (0.09–2.21)	0.31
Total	105	4.7	29	1.7	0.37 (0.25–0.56)	<0.001

CoNS = coagulase negative staphylococci; RR = relative risk.

## Microbiology

Bacterial findings in the 134 (3.4%) patients who received surgical revision are shown in Table IV. The most common primary bacterial agent was monoinfection by CoNS (0.9%) and CoNS with co-infection by *C acnes* (0.7%). Infection with *S aureus* (0.7%) and *C acnes* monoinfection (0.6%) followed. Addition of benzylpenicillin was associated with a significant decrease in SWIs caused by CoNS ( $p < 0.001$ ) and CoNS plus *C acnes* ( $p = 0.008$ ). There was no statistically significant decrease in monoinfection with *C acnes* ( $p = 0.15$ ).

## Discussion

We found that addition of benzylpenicillin to a perioperative prophylactic regimen with cloxacillin significantly reduced the incidence of post-operative SWI after cardiac surgery. The reduction was isolated to DSWI and SWIs that required surgical revision, which are the type of infections where we hypothesized that benzylpenicillin would be most effective since *C acnes* rarely cause superficial SWIs. The reduction occurred promptly when the prophylaxis was changed and remained during the following years. The independent effect of benzylpenicillin was confirmed after adjusting for differences in established risk factors and the use of local gentamicin prophylaxis. Also, two-month mortality in the benzylpenicillin group was slightly lower.

In analogy with previous studies, CoNS was the most common aetiology [5]. The primary aim of adding benzylpenicillin was to address DSWI by *C acnes*. Somewhat surprisingly the most obvious reduction was in SWIs caused by CoNS alone, despite that most CoNS are resistant to benzylpenicillin. Both CoNS and *C acnes* are opportunistic pathogens that cause infection in favourable circumstances, such as skin barrier defects or sternal instability [15]. It could be that *C acnes* and CoNS have a synergistic effect. *C acnes* produce biofilm [12] that might offer a favourable environment for bacterial growth. Both *C acnes* and CoNS have been shown to be present in subcutaneous tissue during cardiac surgery during normal circumstances [11]. There was a significant reduction in SWIs caused by CoNS together with *C acnes*. *C acnes* as the single aetiology was not common and there was no statistically significant reduction in these infections.

Although increasingly reported as a causative aetiology in neurosurgery, in orthopaedic and cardiac surgery *C acnes* may still be overlooked in SSIs for several reasons. The clinical presentation of SSIs caused by *C acnes* is more subtle, with low severity of clinical infection and relatively low increase in white blood cell count and C-reactive protein (CRP) levels [15,22]. *C acnes* takes a long time to culture, between 3 – 27 days anaerobically, and may therefore stay unnoticed if not specifically searched for [22].

Cloxacillin is the recommended prophylaxis for cardiac surgery in Sweden. It is aimed at preventing gram-positive infections, primarily staphylococci. Internationally however, cephalosporins are generally recommended. In contrast to cephalosporins, cloxacillin has no effect on gram-negative bacteria. Despite this, we found almost no gram-negative SWI. This is in agreement with previous results, indicating that intraoperative contamination is not a common mechanism behind infections with gram-negative bacteria. Regarding *C*

*acnes*, cephalosporins were somewhat more effective than cloxacillin in one recent study, although not as effective as benzylpenicillin [10,19], and the effect may differ among the different cephalosporins. Although resistance patterns for *C acnes* vary across the world, benzylpenicillin is generally reported as the most effective antibiotic [10,19].

Addition of vancomycin, intravenously or locally in the sternal wound, has been proposed, especially in environments with high incidence of methicillin resistant staphylococci (MRSA) [16]. However, there may be concerns regarding adverse ecological effects of widespread use of this essential antibiotic. Also, there are side effects associated with use of glycopeptide antibiotics, of which kidney injury is the most feared [17]. The advantages of benzylpenicillin are that it is well tolerated with few side effects; the ecological consequences are less than for many alternatives and it is comparatively inexpensive.

The incidence of DSWIs in our study before the addition of benzylpenicillin was higher compared to some studies [2,4,5,23]. However, it is well known that a majority of SWIs present after discharge [3]. By conducting a systematic two-month follow-up, we were able to detect infections that were treated in other centres or in general practice. Compared to studies with similar follow-up, our SWI-rate was not higher [3,24]. As previously stated, not all of the infections were DSWI, many were only treated with antibiotics.

The use of local collagen gentamicin was independently associated with a decrease in SWI rate, consistent with our previous studies [21,24,25]. Although used by many, this prophylaxis has not reached general acceptance in all centres or countries. The effect of benzylpenicillin was independent of any use of local gentamicin prophylaxis in the multivariable analysis. In other aspects, such as number of sternal wires and all other aspects on wound closure, the technique remained consistent over time.

Although the reduction in CoNS was somewhat surprising, and requires further studies, the reduction mainly in DSWI was completely in line with our prior hypothesis.

We applied a single preoperative dose of benzylpenicillin. Whether or not additional doses during surgery and the first 24 hours, would add further to the effect is unknown. For prevention of infections of implanted valve prostheses or artificial vascular grafts it would be appealing to aim for high concentrations during the entire surgical procedure.

## Limitations

There are obvious limitations of this study. It was a retrospective analysis based on registry data with its inherent limitations. The case-mix of patients changed gradually during the ten-year study period. However, statistical adjustment for potential confounders and differences in baseline data did not change the outcome at all. Furthermore, the reduction in SWI did not occur gradually, but timed very promptly with the change in prophylaxis and the incidence stayed constantly low during the subsequent study period of four years. Early post-operative mortality constitutes a potential competing risk since only patients that are alive develop infections. This was not accounted for in our analyses. However, since mortality was lower in the benzylpenicillin group this would not explain the difference.

Registry data of this cohort did not include information regarding penicillin allergy, therefore these patients could not

be excluded. This could marginally decrease the effect of benzylpenicillin on SWI seen in this study. Frequency of penicillin allergy may be assumed constant over time and proportionally similar in the study groups. In a previous study from our centre the incidence of penicillin allergy (unpublished data) was 3.95%.

## Conclusion

The combination of benzylpenicillin and cloxacillin as peri-operative prophylaxis was associated with a reduced incidence of DSWI compared to cloxacillin monotherapy. The addition of benzylpenicillin could be effective against sternal infection caused by CoNS with and without co-infection by *C. acnes*, although the exact underlying mechanism is unknown.

## Credit author statement

Nadia Sandström: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization.

Anders Magnusson: Formal analysis, Writing - Review & Editing.

Anders Wickbom: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing.

Örjan Friberg: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Supervision.

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## Conflict of interest statement

None.

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## Appendix

**Table A1**

Baseline characteristics and operative factors of excluded patients in cloxacillin (9.4%) and cloxacillin with addition of benzylpenicillin (9.3%) groups.

	Cloxacillin (n = 233)	Cloxacillin and benzylpenicillin (n = 171)	P-value
<b>Risk factors</b>			
Age, y	65 (14)	66 (13)	0.46
Sex, male n (%)	158 (68)	126 (74)	0.20
Weight, kg	81 (16)	83 (17)	0.45
Height, cm	172 (9)	173 (9)	0.41
BMI, kg/m <sup>2</sup>	27 (5)	28 (5)	0.68
P-creatinine, μmol/L	104 (86)	97 (65)	0.84
Additive EuroSCORE	7 (5)	7 (4)	0.74
Smoking <sup>a</sup>	(n=209)	(n=161)	0.83
Never smoked n (%)	86 (41)	68 (42)	
Smoker n (%) <sup>a</sup>	123 (59)	93 (58)	
Diabetes mellitus n (%)	52 (22)	51 (30)	0.10
COPD n (%)	24 (10)	20 (12)	0.63
NYHA class	(n=211)	(n=164)	0.009
I n (%)	31 (15)	20 (12)	
II n (%)	55 (26)	36 (22)	
III n (%)	80 (38)	89 (54)	
IV n (%)	45 (21)	19 (12)	
Steroids/ immunosuppressives n (%)	18 (8)	7 (4)	0.13
<b>Operative factors</b>			
Local Gentamicin n (%)	121 (53)	107 (65)	0.021
Operation time, min	279 (141)	289 (152)	0.009
ECC-time, min	150 (90)	171 (92)	0.001
Aortic cross-clamp, min	93 (54)	111 (60)	0.001
CABG n (%)	112 (48)	94 (55)	0.17
Reexploration for bleeding n (%)	13 (6)	12 (7)	0.37
Single IMA n (%)	61 (26)	46 (27)	0.87
Bilateral IMA n (%)	0 (0.0)	1 (0.6)	0.24
<b>Mortality</b>			
Death before discharge n (%)	51 (22)	28 (16)	0.17
Mortality within two months n (%)	82 (35)	61 (36)	0.95

Figures shown as n (%) or mean (SD). BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ECC = extracorporeal circulation; IMA = internal mammary artery; NYHA = New York Heart Association Functional Classification.

<sup>a</sup> Smoker includes previous smoking.