Local Collagen-Gentamicin for Prevention of Sternal Wound Infections

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Quod scripsi, scripsi.

Versio Vulgata, Ioh. 19:22

To my family

Swedish summary

Inom hjärtkirurgi är infektion i såret efter sternotomin (såret över bröstbenet) alltjämt en av de allvarligaste postoperativa komplikationerna. Koagulasnegativa stafylokocker är numera den vanligast förekommande bakterien vid dessa infektioner. Profylax med intravenöst givet beta-laktam antibiotikum (cefalosporin eller i Sverige vanligen isoxazolylpenicillin) används rutinmässigt. Emellertid är många koagulasnegativa stafylokocker resistenta mot just beta-laktam antibiotika.

Vancomycin är ofta det enda tillgängliga effektiva antibiotikumet för behandling av uppkomna sårinfektioner, men man brukar bestämt avråda från användning av vancomycin som rutinprofylax, bland annat p.g.a. risken för selektion av vancomycinresistenta bakterier.

Målet med detta arbete var att utveckla och utvärdera en ny teknik för antibiotikaprofylax inom hjärtkirurgi. Tekniken består i lokal applicering av gentamicinimpregnerade kollagenplattor i sternotomisåret i tillägg till den vanliga intravenösa antibiotikaprofylaxen.

Antibiotikakoncentrationer i såväl operationssåret som i serum undersöktes, dels efter rutinmässig profylax med intravenöst dikloxacillin och dels efter lokal applicering av kollagen-gentamicin i operationssåret. Dessa studier visade att dikloxacillin-nivåerna var tillräckliga för att förebygga infektioner med methicillin-känsliga stafylokocker samt att extremt höga gentamicinnivåer erhålles i såret under de första 8-12 timmarna efter operationen vid lokal applikation.

Två tusen patienter som genomgick hjärtkirurgi randomiserades därefter till rutinmässig profylax med intravenöst isoxazolyl-penicillin enbart (kontrollgrupp) eller till denna profylax i kombination med inläggning av kollagen-gentamicin plattor (260 mg gentamicin) i sternotomin före sårslutning. Primär end point var förekomst av någon sårinfektion inom två månader efter operationen.

Utvärdering var möjlig i 983 patienter i behandlingsgruppen och 967 i kontrollgruppen. Förekomsten av sårinfektion var 4,3% i behandlingsgruppen och 9,0% i kontrollgruppen (relativ risk = 0,47, (95% konfidensintervall 0,33-0,68); P < 0,001).

Det vanligaste bakteriologiska fyndet vid infektionerna var koagulasnegativa stafylokocker följt av *Stafylococcus aureus*. Lokalt gentamicin reducerade förekomsten av sårinfektioner orsakade av samtliga huvudsakligen förekommande, kliniskt betydelsefulla bakterier utom *Propionibacterium acnes*.

Att tillhöra kontrollgruppen, övervikt, diabetes mellitus, lägre ålder, användande av ena eller båda a mammaria interna, dålig hjärtfunktion (vänster kammares ejektionsfraktion < 35 %) och lång operationstid var oberoende riskfaktorer för att utveckla en postoperativ sårinfektion i en multivariat riskfaktoranalys.

Hos de patienter där man hade använt ytterligare minst en ståltråd (sammanlagt > sex trådar) för att sy ihop bröstbenet var förekomsten av såväl djupa som ytliga sårinfektioner ca 70 % lägre i behandlingsgruppen än i kontrollgruppen och placeringen av kollagenplattorna mellan sternumhalvorna kan fordra att man ägnar särskild uppmärksamhet åt stabiliteten vid fixationen av sternum.

En kostnadseffektivitetsanalys visade att användandet av lokalt kollagen-gentamicin som profylax var dominant, dvs. ledde till såväl färre sårinfektioner som lägre kostnader. Rutinmässig användning av profylaxen till alla vuxna hjärtkirurgipatienter kan förordas.

Abstract

In cardiac surgery, sternal wound infection (SWI) continues to be one of the most serious postoperative complications. Coagulase-negative staphylococci (CoNS) have become the most common causative agents of SWI. Prophylaxis with intravenous beta-lactam antibiotics (cephalosporins or in Sweden most commonly isoxazolyl penicillins) is routinely practised. However, many CoNS species are resistant to beta-lactam antibiotics.

Vancomycin is often the only effective antibiotic available for treatment of these infections, but its use for routine prophylaxis is strongly discouraged because of the risk of increasing the selection of resistant bacteria.

The aim of this work was to develop and evaluate a new technique for antibiotic prophylaxis in cardiac surgery consisting of application of drug eluting collagen-gentamicin sponges in the sternal wound in addition to conventional intravenous antibiotics.

The antibiotic concentrations in the wound and serum achieved by routine intravenous dicloxacillin prophylaxis and those after application of local collagen-gentamicin in the sternal wound were investigated. These studies showed dicloxacillin levels adequate for prevention of infections by methicillin-susceptible staphylococci, and extremely high gentamicin levels in the wound fluid, during the first 8-12 hours postoperatively with the local application.

Two thousand cardiac surgery patients were then randomised to routine prophylaxis with intravenous isoxazolyl penicillin alone (control group) or to this prophylaxis combined with application of collagen-gentamicin (260 mg gentamicin) sponges within the sternotomy before wound closure. The primary end-point was any sternal wound infection within two months postoperatively.

Evaluation was possible in 983 and 967 patients in the treatment and control groups, respectively. The incidence of any sternal wound infection was 4.3% in the treatment group and 9.0% in the control group (relative risk = 0.47, (95% confidence interval 0.33 to 0.68); P<0.001).

The most common microbiological agents were CoNS, followed by *Staphylococcus aureus*. Local gentamicin reduced the incidence of SWIs caused by all major, clinically important microbiological agents except *Propionibacterium acnes*.

Assignment to the control group, high body mass index, diabetes mellitus, younger age, single or double internal mammary artery, left ventricular ejection fraction less than 35% and longer operation time were independent risk factors for SWI in a multivariable risk factor analysis.

In patients with additional sternal fixation wires (> six wires) the collagen-gentamicin prophylaxis was associated with an approximately 70 % reduction in the incidence of SWI at all depths and the application of collagen sponges between sternal halves may require particular attention regarding the stability of fixation.

A cost effectiveness analysis showed that the application of local collagen-gentamicin as prophylaxis was dominant, i.e. resulted in both lower costs and fewer wound infections.

Routine use of the described prophylaxis in all adult cardiac surgery patients could be recommended.

List of papers

- I Friberg Ö, Jones I, Sjöberg L, Söderquist B, Vikerfors T, Källman J. Antibiotic concentrations in serum and wound fluid after local gentamicin or intravenous dicloxacillin prophylaxis in cardiac surgery. Scand J Infect Dis 2003;35(4):251-4.
- II Friberg Ö, Svedjeholm R, Söderquist B, Granfeldt H, Vikerfors T, Källman J. Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial. Ann Thorac Surg 2005;79(1):153-61.
- III Friberg Ö, Dahlin L-G, Levin L-Å, Magnusson A, Granfeldt H, Källman J, Svedjeholm R. Cost effectiveness of local collagen-gentamicin as prophylaxis for sternal wound infections in different risk groups. Scand Cardiovasc J 2005:doi:10.1080/14017430500363024.
- IV Friberg Ö, Svedjeholm R, Källman J, Söderquist B. Incidence, microbiological findings and clinical presentation of sternal wound infections after cardiac surgery with and without local gentamicin prophylaxis. *Submitted*
- V Friberg Ö, Dahlin L-G, Söderquist B, Källman J, Svedjeholm R. Reduced deep sternal wound infection rate in patients with more than six sternal fixation wires and local collagen-gentamicin as prophylaxis. *Submitted*

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Abbreviations

BMI body mass index (kg/m²)

CABG coronary artery bypass grafting

CDC Centers for Disease Control and Prevention (United States Department of Health &

Human Services)

CFU colony-forming units
CI confidence interval

CoNS coagulase-negative staphylococcus COPD chronic obstructive pulmonary disease

CPB cardiopulmonary bypass (~ECC)

CRP C-reactive protein

CT computerised tomography

DM diabetes mellitus

DSWI deep sternal wound infection ECC extracorporeal circulation

€ euro

HLGR high-level gentamicin-resistance

ICU intensive care unit

IMA internal mammary artery

iv intravenous

LVEF left ventricular ejection fraction
MIC minimal inhibitory concentration

MRSA methicillin-resistant staphylococcus aureus

MRSE methicillin-resistant staphylococcus epidermidis (a CoNS)

OR odds ratio

RCT randomised controlled trial

RR relative risk

SD standard deviation SSI surgical site infection

SSWI superficial sternal wound infection

SWI sternal wound infection

VRSA vancomycin-resistant staphylococcus aureus

WHO World Health Organisation

Surgical site infection (SSI) is the most common nosocomial infection among surgical patients(1). The impact of these infections in terms of clinical and financial outcomes is substantial. In a recent analysis of the burden of *Staphylococcus aureus* infections in US hospitals during the years 2000 and 2001 it was concluded that these infections alone cause almost 12 000 in-patient deaths and an estimated 2.7 million days in excess length of stay in the US annually (2). In patients who had undergone invasive cardiovascular surgery a *S. aureus* infection accounted for an increase in hospital charges of +67 499 US\$ compared to in-patients without *S. aureus*. How many of these were wound infections was not specified. However, postoperative sternal wound infections (SWI) can be expected to constitute a substantial proportion of – and to be among the most severe – *S. aureus* infections in cardiothoracic patients.

Incidence of sternal wound infection

Sternal wound infection is a well-known complication after cardiac surgery. The reported incidence varies from 0.25 to 9% (3-9). The large differences in the reported incidence probably reflect inconsistency in definition, classification, and completeness of the post-operative follow-up. In the few studies that provide detailed information regarding how a complete postoperative follow-up and data collection were achieved the total incidence of SWI was about 6 - 9% (3, 10, 11).

Definitions and classifications

There are several systems for classification of surgical wound infections. The Centers for Disease Control and Prevention (CDC) system for classifying a postoperative SSI is the most one commonly referred to (1). Briefly, it incorporates infections occurring within 30 days after the operation and *defines* an infection according to relatively liberal criteria (e.g. positive culture or purulent drainage or evidence of deep infection on radiological or histopathological or other examination or – notably – diagnosis of a SSI by a surgeon or attending physician). The infections are then *classified* based on the *depth* into Superficial incisional SSI, Deep incisional SSI or Organ/Space SSI.

Cardiothoracic surgeons, however, have not commonly used the CDC classification. One reason for this might be that it is not intuitively easy to apply to sternal wound infections, since the term "deep" wound infection has by tradition mostly been used for cases with sternal instability and/or an apparent abscess in the mediastinum, whereas the CDC system classifies all infections below the superficial fascia as deep, thus including infections superficial to the sternum but reaching down to the sternal fixation wires. In cardiothoracic literature the term mediastinitis is often used synonymously with deep SWI (DSWI). However, the term mediastinitis is poorly defined and some of the infections classified as deep in the CDC system would not be classified as mediastinitis in most reports from cardiothoracic institutions.

Further confusion is caused by the fact that there are cases of sternal dehiscence, caused by primary "mechanical instability", without a primary wound infection. To what extent these cases have appropriate bacterial samples taken to detect a bacterial component or just undergo surgical refixation (sometimes with short "prophylactic" antibiotic regimens) and to what extent they are reported at all, probably vary greatly between institutions.

There are also data suggesting that any mechanical instability will promote the growth of bacteria present in the wound and unless the wound is promptly stabilized, a clinical wound infection will develop (12). It is also well recognised that a fulminant SWI without early surgical treatment will rapidly lead to sternal bone destruction with subsequent dehiscence.

Early surgical intervention in both these cases can prevent the development of more serious consequences. On the other hand it will imply an increased incidence of surgical interventions, which may give a false impression of an increased rate of SWIs.

Some airborne bacterial contamination of surgical wounds is unavoidable and it is conceivable that at the end of a cardiac operation there may be bacteria present in the surgical wound in a majority of cases (13, 14). Nevertheless, few of these patients develop clinical wound infections requiring antibiotic or surgical treatment.

Thus, neither the presence of bacteria in a wound nor sternal dehiscence should constitute sole criteria for a diagnosis of SWI, and some degree of subjectivity in the interpretation of culture samples and in the definition is unavoidable. For comparison of the incidence of SWI between units and between different time periods the number of patients who have experienced *any* kind of problem with wound healing will be a fairly objective parameter, presuming that all patients are followed up for at least 30 days, or preferably longer.

El Oakely et al have presented a classification of verified cases of mediastinitis (15) based on the presence or absence of certain risk factors and also on whether it is the first mediastinitis or the "second" one after a failed attempt to treat the first. There are no strict criteria, however, for the definition of a mediastinitis.

The ASEPSIS score, developed and presented by Wilson et al, is well-defined and probably the most scientifically and clinically relevant classification system available today (10). It sets a score based on both local symptoms and treatments of a wound infection, thus measuring the clinical "severity" of the infection irrespective of its depth or other characteristics. It is time consuming, since it involves a thorough follow-up of all wounds postoperatively for a period of two months. Unfortunately, it has not been generally used in research. This may be due to the facts that most published reports are based on retrospective analyses and the meticulous follow-up and documentation of all surgical wounds is not commonly implemented in clinical practice.

Microbiology

Coagulase-negative staphylococci (CoNS), mostly *Staphylococcus epidermidis*, have emerged as the most common pathogenic agents during the last 20 years, followed by the previously dominating bacterial agents *S. aureus* and Gram-negative bacteria (5, 6, 16-19). *Propionibacterium acnes* has also been reported recently as a relatively common agent (16). Formerly probably regarded as a mostly harmless contaminant, its role, however, in postoperative SWI is still unclear. Less commonly reported agents include streptococci, anaerobic bacteria, *Candida albicans*, Aspergillus and mycobacterium tuberculosis (16, 20-25)

The three dominating agents, CoNS, *S. aureus* and Gram-negative rods, have been reported to be associated with different clinical characteristics of the mediastinitis and possibly with different pathogenetic mechanisms (19). Mediastinitis caused by CoNS has been claimed, for example, to be associated with obesity, chronic obstructive pulmonary disease (COPD) and sternal dehiscence, mediastinitis caused by *S. aureus* has been proposed to be caused by intraoperative contamination of the mediastinum, and Gram-negative rods are reported

to be mainly found in mediastinitis caused by spread from concomitant infections in other sites during the postoperative period. This classification is interesting since it entails the use of different prophylactic measures to address the different agents and pathogenetic mechanisms.

Mortality

There is considerable variation in the reported early mortality due to SWI. Most centres have reported mortality rates of about 10-30%, although some authors report zero, or almost zero mortality when applying new treatment modalities (7, 26-29). The mortality seems to have decreased gradually during the last 20 years. There may be a selection bias towards more serious infections in the earlier series and series presenting low total incidences of SWI. There is a risk, not always recognised, of underestimating the consequences of an SWI when comparing mortality in these cases with that in uninfected matched or unmatched controls, since there is a selection bias (i.e. only patients who survive are at risk of developing an SWI).

Furthermore, the detrimental effect of SWI may extend far beyond the in-hospital and 30-day period and mediastinitis has been reported to be associated with a marked decrease in long-term survival (30, 31) (32).

Cost

The cost of a SWI has been estimated to be about 14 000 – 40 000 US\$. A short summary of estimations of the cost published since 1990 is given in Table 1. The costs cannot be directly compared, since they refer to different time periods and, in addition, the calculations may be less valid when applied on different countries with different health care systems. Most investigators compare infected patients with non-infected controls. However, case-control studies may be biased. The controls need to be carefully matched, since most risk factors for infection (e.g. low left ventricular ejection fraction [LVEF], high body mass index [BMI], diabetes mellitus [DM]) are also risk factors for other postoperative complications leading to increased costs.

Nevertheless, it is unquestionable that the cost of treating a postoperative SWI is substantial. Furthermore, all of the studies listed in Table 1 include only costs for the health care provider and no indirect costs for society, costs for the patient or economic calculations of losses in quality of life, for example.

Prevention

Since the costs of SWI for the health care system are high and the consequences for the patient potentially devastating, even comparatively expensive but effective prophylactic measures can be justified and actually cost saving.

Avoidance of cardiac surgery in patients with an increased risk of infection is rarely an option, especially since important risk factors (e.g. DM, high BMI) are also risk factors for cardiovascular disease and some risk factors (e.g. DM, low LVEF) are correlated to a better general outcome with surgery compared with medical or alternative treatments. There are, however, a large number of controllable aspects that influence the rate of SWI. It should be emphasised that effective prevention requires that all these aspects be addressed simultaneously.

Table 1. Calculated costs for the treatment of a postoperative sternal wound infection

Reference	Cost	Specification of cost	Comments
Hollenbeak CS, Murphy DM, Koenig S, Woodward	US\$ 20 012	by case control	USA, large midwestern community medical centre. Consecutive
RS, Dunagan WC, Fraser VJ. The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. Chest 2000;118:397-402		deep sternal wound infection according to CDC classification	CABG patients 1996-1998. Unmatched case-control study. Cost of surgical site infection was also calculated by multiple linear regression to control for factors other than surgical site infections that may have an independent effect on cost of care.
	US\$ 18 938	by multivariate regression	,
Hollenbeak CS, Murphy D, Dunagan WC, Fraser VJ. Nonrandom selection and the attributable cost of surgical-site infections. Infect Control Hosp Epidemiol 2002;23:177-82	US\$ 14 211		Same material as above, analysed with "Heckman's two stage approach" to control for selection bias.
Jenney AW, Harrington GA, Russo PL, Spelman DW. Cost of surgical site infections following coronary artery bypass surgery. ANZ J Surg 2001;71:662-4.	\$AU 12 419*	all wound infections inclu- ding donor site infections	Australia, consecutive CABG patients 1996-1998. Case-control (matched 1:1) study. The authors consider that their approximations "certainly underestimate the true cost" due for example to the fact that
	\$AU 31 597	deep sternal wound infections only	the cost of reoperations was not included in the analysis.
Loop FD, Lytle BW, Cosgrove DM, et al. J. Maxwell Chamberlain memorial paper. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. Ann Thorac Surg 1990;49:179-86	≥ US\$ 30 000(?)	wound complication ("mediastinitis, dehiscence or both")	USA (Cleveland Clinic). Retrospective. 6504 consecutive patients 1985-1987. Compared hospital charges for all patients with no complications with those of the 72 patients with wound complications. Presented in 1987 dollars. Result presented as: "median charge \$58,092 (\$16,966 to \$ 408,632) which was 2.8 times that of uncomplicated cases."
Mauldin PD, Weintraub WS, Becker ER. Predicting hospital costs for first-time coronary artery bypass grafting from preoperative and postoperative variables. Am J Cardiol 1994;74:772-5	US\$ 25 230	wound infection	USA, Emory University, Georgia. 807 consecutive CABG patients 1990. Impact of several preoperative and postoperative variables (univariate) on hospital costs. No details from the multivariate analysis. (That there were only 5 infections in the material may make estimate uncertain)
Taylor GJ, Mikell FL, Moses HW, et al. Determinants of hospital charges for coronary artery bypass surgery: the economic consequences of postoperative complications. Am J Cardiol 1990;65:309-13	US\$ 41 559	sternal infection	USA, St Johns Hospital, Illinois. 500 consecutive CABG patients 1985. Multivariate regression analysis on the impact of several postoperative complications on the cost of the care.

*1 \$AU \sim 0.66 US\$ in 1998 CDC = Centers for Disease Control and Prevention; SWI=Sternal Wound Infection

1. Minimise contamination

a. Reduce bacterial levels in the operating room

The number of bacteria in the air in the operating room, measured as colony-forming units (CFU)/m², has been shown to correlate to the rate of wound infections and there are recommendations for acceptable counts of CFU/m² for different types of surgery (33, 34). The level of CFU/m² is influenced by the type of ventilation system in the operating room and can also be reduced by letting the staff wear tightly woven clean air suits instead of cotton suits (35, 36). The clothes worn by the staff in the operating room should not be used in contact with patients elsewhere. Staff with any skin infection should not be allowed in the operating room (37).

Also, ultraviolet radiation has been shown to reduce the airborne contamination (38).

b. Pre- and postoperative hygiene routines

Preoperative chlorhexidine disinfection of the patients skin has been shown to reduce the skin flora but not to reduce the number of wound infections in a randomised controlled trial (RCT) (39). Nevertheless, preoperative showering with chlorhexidine is commonly practised. The patient's nasal carriage of *S. aureus* has been identified as an important source of bacterial contamination and a risk factor for the development of a postoperative wound infection, and elimination of nasal carriage reduce the incidence of wound infections (40-43).

Preoperative shaving of the surgical site the night before an operation is associated with a significantly higher risk of SSI than either the use of a depilatory agent or no hair removal (1). If the hair on the incision site is to be shortened preoperatively, this should be done immediately before surgery, not the night before, and it should be done with a clipper, without shaving (44).

The spread of pathogenic or resistant bacterial strains between patients and staff in the ward can be minimised through strict hygiene routines.

2. Surgical technique

a. Avoid necrosis and ischaemia

Impaired blood supply is one of the fundamental causes of delayed healing in all kinds of surgery and is the proposed mechanism by which usage of one or both internal mammary arteries in coronary bypass surgery (CABG) is associated with an increased risk for SWI (6, 8, 27, 45).

Discriminate use of electrocautery on presternal tissue has been shown to decrease the incidence of wound infection in dogs, and systematic use of the technique has been reported to be associated with a low incidence of mediastinitis in humans (46, 47).

b. Avoid haematomas, bleeding and dead space

Cavities or haematomas constitute spaces and substrates for bacterial growth that is uninhibited by the immune system and is hard to reach with antibiotic prophylaxis. Bleeding is also associated with red cell transfusion and reoperation, two reported risk factors for SWI (48, 49). Most studies of the risks of SWI related to red cell transfusion have been carried out on conventional red blood cell concentrates. However, transfusion with filtered, leucocyte-free red blood cell concentrates may carry a substantially lower risk.

c. Rigid fixation of bone and tissues

In orthopaedic surgery, stable, rigid fixation of fractures has been shown to reduce the infection rate, despite the presence of foreign material, in both experimental and clinical studies (12, 50, 51). In cardiac surgery, a prospective randomised trial demonstrated a lower incidence of SWI with a modified technique of reinforced sternal fixation and other reports have also supported the theory that additional measures to achieve rigid sternal fixation reduce the incidence of SWI (52-55).

d. Minimise foreign material

Adherence to foreign materials is one important pathogenetic property of e.g. CoNS (56). Avoidance of permanent or long-term implantation of iv catheters, suture material and so on can therefore be advocated.

3. Optimise conditions for wound healing

a. Optimise blood supply and pO, in tissues

Low LVEF and the use of (mostly adrenergic) inotropic support with a consequently reduced peripheral blood flow are commonly reported risk factors for SWI (6, 17, 28, 57, 58). A large randomised study in colorectal surgery patients showed a significant reduction of the surgical wound infection rate when patients received 80% oxygen during surgery and 2 hours postoperatively, compared to 30% in the control group (59). This effect was confirmed in a recent study (60) and although conflicting results have been reported from other studies (these were smaller and have been methodologically criticised (61, 62)), there is growing evidence that supplemental oxygen reduces the incidence of SSI after colorectal surgery and deserves further evaluation in other surgical procedures.

b. Reduce oedema

Oedema, caused for example by volume overload, right-sided heart failure or increased capillary permeability, may reduce tissue perfusion and impair wound healing. A randomised study in abdominal surgery showed that wound healing improved when intravenous fluid was restricted perioperatively (63).

c. Optimise blood glucose control

Strict control of blood glucose levels reduces the rate of deep wound infection and also of mortality in diabetics undergoing cardiac surgery (64, 65). Intensive insulin treatment in the intensive care unit (ICU) has been shown to reduce mortality and morbidity, including septic complications, regardless of whether the patients have a history of diabetes or not (66). The mechanisms underlying these effects are not fully understood and the influence both of glycaemic control and of increased insulin levels may be contributory. Inactivation of proteins involved in the immune system and wound healing by glycosylation, as well as deterioration of leucocyte function, are related to an elevation in blood glucose.

4. Antibiotic prophylaxis

Aim of the prophylaxis

Antibiotic prophylaxis in cardiac surgery appears to have been initially focused mainly on prevention of endocarditis and prosthetic valve infections. Several studies have addressed concentrations of antibiotics in the serum and in cardiac tissue but there are fewer data on concentrations in the wound (67-72). With the expansion of coronary bypass surgery 25-30 years ago the aim seems to have changed mainly to prevention of sternal wound infections.

Intravenous prophylaxis

A number of randomised studies have shown that perioperative intravenous prophylaxis reduces the wound infection rate to about 1/5 compared with placebo(73). This doubtless makes it the single most effective preventive action, compared with those previously mentioned. The timing of the prophylaxis is important (74). The systemic antibiotic concentration should already be high at skin incision and kept high during surgery. There is no evidence that extension of the prophylaxis postoperatively provides any benefit and there are economic and ecological reasons why the prophylaxis should be kept short. Use of prophylaxis of less than 48 hours' duration is now generally accepted (1, 75-78). In fact, a duration of <24 hours has been recommended and to extend the prophylaxis until all catheters and drainage tubes have been removed cannot be considered appropriate (79-82).

Beta-lactam antibiotics are most frequently used (77, 78). In Sweden isoxazolylpenicillins are most common. They have an excellent effect on methicillin-susceptible staphylococci but no effect on Gram-negative bacteria. However, since the latter infections are less common and the relative incidence of Gram-negative agents among SWI in Sweden has been generally lower than figures reported from the United States, this prophylaxis has been considered satisfactory in our country. Internationally, cephalosporins are completely dominating as the recommended prophylaxis (78, 83, 84), the rationale being their broader spectrum with an effect on Gram-negative microorganisms. In some countries, for example England, cephalosporins have occasionally been combined with it aminoglycosides (77). However, no significant additional effect of this iv combination, compared with that of cephalosporins alone, has been reported (79, 85, 86).

Although the pharmacokinetics of beta-lactams in the blood and different tissues is well known, there are few studies on this subject in patients during extracorporeal circulation (ECC; heart-lung machine) and even fewer on the concentrations of antibiotics in the mediastinal fluid after cardiac surgery. There are no reported data on the systemic concentrations of dicloxacillin in cardiac surgery. For several reasons, including the direct contact of the patient's blood with the foreign material in the oxygenator and tubes, the instant haemodilution caused by the priming fluid in the ECC circuit, and the frequent intra- and postoperative disturbance of renal function, the pharmacokinetics of drugs during and after cardiac surgery may differ from the "normal".

Rationale for reconsidering the present iv prophylaxis

A major limitation of the present prophylaxis in cardiac surgery is that many CoNS – the most common causative agent – are resistant to beta-lactam antibiotics. These strains are commonly referred to as methicillin-resistant *S. epidermidis* (MRSE). Methicillin-resistant *S. aureus* (MRSA) has also emerged as a potential pathogen in postoperative SWI (87, 88).

Vancomycin is often the only effective antibiotic available for treatment of sternal infections caused by these agents, but its use for routine prophylaxis is strongly discouraged by microbiologists because of the risk of increasing the selection of resistant bacteria with subsequent serious ecological and therapeutic consequences. The importance of restrictive use of vancomycin is emphasised by recent reports from France of MRSA with reduced susceptibility to glycopeptides (89, 90). *S. aureus* with reduced susceptibility to vancomycin was first reported in 1997 (91), and in 2002 a clinical isolate of vancomycin-resistant *S. aureus* (VRSA) (minimal inhibitory concentration [MIC], >32 μg/mL) was identified (92).

In addition, vancomycin is a less active anti-staphylococcal agent than are beta-lactam anti-biotics (93), and its effects on MRSE and MRSA may not compensate for a weaker effect on methicillin-susceptible staphylococci. Accordingly, in a meta-analysis iv glycopeptides were in fact found to be inferior to beta-lactam antibiotics in preventing SWI after cardiac surgery (94) and vancomycin was not superior even in a study conducted in a centre with high prevalence of MRSA (95).

Hence, alternative approaches to prevention of postoperative sternal infections need to be explored.

Local application of antibiotics

Local administration of gentamicin is a theoretically appealing way of achieving very high local antibiotic concentrations, far beyond what would have been possible by systemic administration in view of the risk of toxic adverse reactions. Hence, the high gentamicin concentration in the wound achieved by local application of gentamicin may be effective against bacteria that are normally considered resistant according to the MIC values. Topical gentamicin has been successfully used in treatment of mediastinitis and as prophylaxis in abdominal surgery (96, 97). Gentamicin has, moreover, a long tradition in orthopaedic surgery, being added to bone cement as prophylaxis and being used in the treatment of osteomyelitis.

Although gentamicin is generally used for Gram-negative infections, it does have a spectrum of bactericidal activity against many Gram-positive organisms, including staphylococci (98). Synergism between aminoglycosides and beta-lactam antibiotics has also been reported (99), and the addition of a single 5 mg/kg iv gentamicin dose to vancomycin or daptomycin has been reported to increase the bactericidal activity against MRSA (100). Topical vancomycin has been shown to reduce the incidence of sternal infection in one randomised study (101). However, although frequently practised (84), all prophylactic use of vancomycin should be restrictive, for the reasons previously mentioned.

Aims

The aim of this work was to develop and evaluate a new technique for antibiotic prophylaxis in cardiac surgery consisting of insertion of absorbable, drug eluting collagengentamicin sponges in the sternal wound in addition to the conventional iv antibiotics.

The specific aims of this thesis were:

- to investigate the antibiotic concentrations in the wound and in the serum achieved by routine iv administration of dicloxacillin (paper I)
- to determine the antibiotic concentrations in the wound and serum achieved by application of local collagen-gentamicin in the sternal wound (paper I)
- to evaluate the effect of addition of local collagen-gentamicin as prophylaxis on the incidence of postoperative SWI (paper II)
- to identify and analyse risk factors for SWI and any possible heterogeneity of the effect of the prophylaxis in relation to these risk factors (papers II and III)
- to assess the cost effectiveness of local collagen-gentamicin prophylaxis (paper III)
- to examine the microbiological findings in SWIs in relation to the clinical presentation of these infections and the effect of the prophylaxis (paper IV)
- to test the post-hoc hypothesis that sternal closure with six or fewer sternal wires was associated with a weaker effect of the local gentamicin prophylaxis on DSWI (paper V).

Materials and Methods

Patients

Dicloxacillin concentrations after iv administration (I)

One hundred and one consecutive adult cardiac surgery patients without penicillin intolerance were included (Table 2) and received iv dicloxacillin according to the routine protocol; see below.

Gentamicin concentrations after local administration (I)

The gentamicin concentrations in the serum and wound were measured in 30 consecutive cardiac surgery patients who had received routine iv prophylaxis with dicloxacillin combined with sternal application of collagen-gentamicin; see below (Table 2). Renal insufficiency was not an exclusion criterion, and one patient had been bilaterally nephrectomised and was on haemodialysis.

Table 2. Patient characteristics in antibiotic concentration studies.

	Iv dicloxacillin (n=101)	Local gentamicin (n=30)
Sex (M/F)	70/31	25/5
Operation		
CABG	74	28
Valve	12	1
CABG+valve	12	
Other	3	1
Age (yr)	67.1 ± 8.9 (37–80)	64.6 ± 9.0 (46–79)
Weight (kg)	$77.8 \pm 13.0 \ (44-106)$	$80.2 \pm 13.9 (50-123)$
S-creatinine (µmol/L)	94.7 ± 20.9 (30–176)	111.3 ± 106.5 (70–669)

Data are shown as numbers of patients (n) or mean +/SD (range).

CABG = coronary artery bypass grafting.

Local Gentamicin for Sternal Wound Infection Prophylaxis (LOGIP) trial (II-V)

The study was conducted in two cardiothoracic centres (Centres A and B) in Sweden during the period September 2000 to September 2002.

Eligible for inclusion in the study were all patients undergoing cardiac surgery through median sternotomy, including operations on the ascending aorta. Exclusion criteria were: 1) known allergy to gentamicin, 2) pregnancy or breast-feeding, 3) treatment with aminoglycosides during the last 2 weeks before surgery, and 4) expected difficulty in fulfilling the follow-up requirements, for linguistic or other reason.

During the study period a total of 2742 patients underwent cardiac surgery at the two centres. Two thousand eligible patients were identified and preliminarily included (Fig. 1). Of these, 1956 patients entered the study. Six of these could not be reached at the follow-up. Table 3 shows baseline data of the remaining 1950 patients and of all other patients operated on during the study period (including those excluded during the trial process).

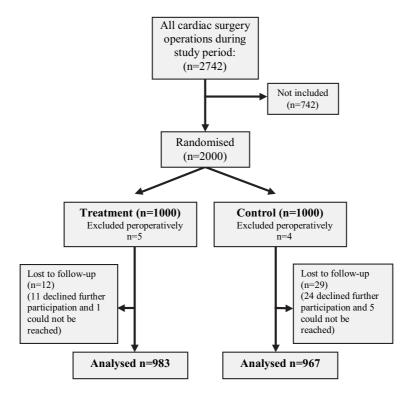


Figure 1. Trial profile, LOGIP trial

Materials and Methods

Table 3. Baseline data, LOGIP trial

		Control	Treatment	All other opera- tions during
		(n = 967)	(n = 983)	study period* (n = 792)
Centre, no. of patients ((%)			
Centre A		503 (52.0)	509 (51.8)	363 (45.8)
Centre B		464 (48.0)	474 (48.2)	429 (54.2)
Sex				
Male, no. (%)		735 (76.0)	753 (76.6)	525 (66.3)
Age in years, median (ra	ange)	68 (20-87)	68 (25-87)	70 (16-88)
Risk factors				
BMI, median (range)	26.6 (14.8-46.1)	26.3 (15.6-42.8)	
Serum creatinine (µ	mol/L), median (range)	94 (50-1084)	96 (45-801)	
Preop dialysis, no. (%)	9 (0.9)	5 (0.5)	
Diabetes, insulin/drug treated, no. (%)		174 (18.0)	180 (18.3)	154 (19.4)
COPD, no (%)		58 (6.0)	52 (5.3)	55 (6.9)
Left ventricular ejection fraction <35%, no. (%)		65 (6.7)	50 (5.1)	37 (4.7)
Preop medication: n	o. (%)			
Oral steroid treats	ment	47 (4.9)	22 (2.2)	
Immunosuppressi	ion	12 (1.2)	9 (0.9)	
Preop anticoagulation, any		570 (58.9)	622 (63.3)	
Dalteparin or Heparin (within 24 h)		338 (35.0)	347 (35.3)	
Warfarin (within 3 days)		9 (0.9)	9 (0.9)	
Clopidogrel (within 3 days)		11 (1.1)	9 (0.9)	
Aspirin (within		465 (48.1)	536 (54.5)	
Dipyridamole		6 (0.9)	3 (0.3)	
Preop hospital stay,	days, median (range)	1 (0-40)	1 (0-41)	
Emergency operation, no. (%)		23 (2.4)	23 (2.3)	97 (12.2)
Type of surgery, no. (%	(o)			
CABG		698(72.2)	732 (74.5)	555 (70.1)
Off pump (% of C	CABG)	63 (9.0)	65 (8.9)	51 (9.2)
Valve	•	135 (14.0)	131 (13.3)	108 (13.6)
Aortic aneurysm		18 (1.9)	11 (1.1)	48 (6.0)
Congenital malform	ation	5 (0.5)	6 (0.6)	4 (0.5)
CABG+other (mostl		100 (10.3)	95 (9.7)	66 (8.3)
Other	,	11 (1.1)	8 (0.8)	11 (1.4)
Use of mammary arte	ery, no. (%)			
LIMA only	all operations	679 (70.2)	701 (71.3)	
•	CABG(% of CABG)	615 (88.1)	641 (87.6)	
RIMA only	all operations	4 (0.4)	6 (0.6)	
,	CABG(% of CABG)	3 (0.4)	5 (0.6)	
Bilateral IMA	· · · · · · · · · · · · · · · · · · ·	10 (1.0)	9 (0.9)	
	CABG(% of CABG)	9 (1.3)	9 (1.2)	
Times, minutes				
Operation, duration,	median (range)	195 (65-632)	195 (60-778)	
CPB, duration, medi		88 (19-365)	87 (30-480)	91 (22-619)

^{*}Consists of 742 patients never included and the 50 patients excluded from the study; only data retrievable from the centres' clinical databases are shown for these patients. BMI = body mass index (kg/m2), CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, CPB = cardiopulmonary bypass, LIMA/RIMA = left/right internal mammary artery.

Analyses of the influence of additional sternal fixation wires (V)

In paper V, subpopulations of the LOGIP patient population were studied as follows: Patients operated on at centre A were subdivided on the basis of the number of fixation wires used for sternal closure into those with six or fewer sternal fixation wires (standard technique, ST group) and those with seven or more fixation wires (extra wire technique, XW group). There were 1012 patients in the trial from centre A and the number of wires was available for 1005 of these patients (Table 4).

The baseline data of the two groups did not differ significantly, except that the patients in the XW-group had a slightly higher mean height (Table 2 in Paper V).

		I	r
No of sternal wires	n (%)	Group	n (%)
5	10 (1.0)	"ST"	741 (72.7)
6	731 (72.2)	(standard technique)	741 (73.7)
7	235 (23.2)	•••••	•
8	27 (2.7)	"XW"	2(4(2(3)
9	1 (0.1)	(extra wires)	264 (26.3)
10	1 (0.1)		

Table 4. Number of sternal fixation wires used in 1005 of the 1012 patients operated on at centre A.

The effect of the collagen-gentamicin prophylaxis was analysed with the ST group excluded from the total study population (Fig. 2). Of the remaining 1 202 patients, 613 and 589 were randomised to the treatment and control groups, respectively. Table 5 shows baseline data of these patients.

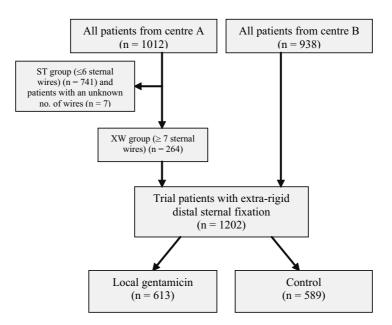


Figure 2. All patients from centre B and those patients from centre A with 7 or more sternal wires (the extra wire [XW] group) constituted the group of patients in the original LOGIP trial that were considered to have extra-rigid distal sternal fixation.

ST = Standard technique

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Table 5. Baseline data of the 1 202 cardiac surgery patients in the LOGIP trial remaining after exclusion of patients at centre A with six or fewer sternal wires. In the treatment group collagengentamicin (260 mg gentamicin) was applied in the sternal wound. All differences between the two groups are non-significant

	Treatment	Control
	(n = 613)	(n = 589)
Type of surgery, No. (%)		
CABG	459 (74.9)	413 (70.1)
Valve	82 (13.4)	89 (15.1)
CABG + other	54 (8.8)	58 (9.8)
Aortic aneurysm	9 (1.5)	16 (2.7)
Congenital malformations	4 (0.7)	2 (0.3)
Other	5 (0.8)	11 (1.9)
Risk factors		
Continuous, mean (SD)		
BMI, kg/m^2	26.8 (3.7)	26.8 (4.1)
Age, yr	65.9 (10.1)	65.8 (10.5)
Duration of operation, min	205 (59.9)	207 (68.7)
Categorical, No. (%)		
Diabetes	104 (17.0)	101 (17.1)
Unilateral IMA	442 (72.1)	402 (68.3)
Bilateral IMA	6 (1.0)	5 (0.8)
LVEF <35%	25 (4.1)	35 (5.9)
Immunosuppression	6 (1.0)	9 (1.5)
COPD	29 (4.7)	34 (5.8)

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; IMA = internal mammary artery; LVEF = left ventricular ejection fraction.

SD = standard deviation.

Antibiotic prophylactic techniques

Routine iv antibiotic prophylaxis protocol

Dicloxacillin was given at an iv dose of 1g at the following times: immediately before skin incision; after 2 h of operating time; immediately before sternal closure (unless it had been given within the last 2 h); and postoperatively every 8 h. During the concentration studies (paper I) it was continued until the morning of postoperative day 2, i.e. 36–48 h postoperatively.

During the LOGIP trial (paper II-V), iv antibiotic prophylaxis was discontinued after 24 hours. At the second participating centre (centre B) cloxacillin, 2 g, was given at similar intervals. Patients with penicillin intolerance received clindamycin 600 mg at similar intervals.

Local collagen-gentamicin: surgical technique

Collatamp®-G (at the time of the study marketed by Schering-Plough, Stockholm, Sweden; at present by Innocoll Pharmaceuticals, Athlone, Ireland) consists of a flat absorbable bovine collagen sponge impregnated with gentamicin sulphate. A 10x10x0.5 cm sponge contains 280 mg collagen and 130 mg gentamicin (200 mg gentamicin sulphate). At the end of the operation, two sponges were cut into pieces of appropriate sizes (approximately 5x10 cm) that were placed between the sternal halves before the sternal wires were tightened (Fig. 3). The sternum was closed with 6-8 steel fixation wires. The wires were put around the sternum in the intercostal spaces at the level of the corpus and as a rule transsternally at the manubrium.

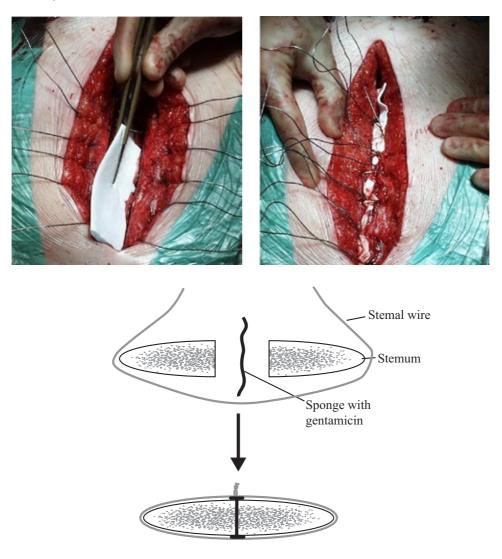


Figure 3. The collagen sponges were placed in a single layer between the sternal halves before the wires were tightened.

Study design and data collection

Antibiotic concentrations in serum and wound fluid (I)

Dicloxacillin concentrations (I)

Venous blood (serum) samples for measurement of dicloxacillin concentrations were taken at sternal closure. Samples from the mediastinal (pericardial) fluid were taken at sternal closure and then from the chest tubes immediately before each successive dicloxacillin dose as long as the chest tube drainages were still in place.

Gentamicin concentrations (I)

Gentamicin concentrations were measured in drainage fluid from the chest tubes and in venous blood (serum) postoperatively at 2, 4, 8 and 12 h and at 2, 4, 8, 12, 24 and 48 h after sternal closure, respectively.

Design of the LOGIP trial (II-V)

General design

The study was randomised, prospective and double-blind (i.e. the patients and those physicians and nurses who collected all the postoperative data and classified the infections were blinded regarding what treatment the patients had received).

At the end of the operation, immediately before sternal closure, the patient was allocated to a treatment group (routine iv prophylaxis combined with sternal application of collagen-gentamicin; see above) or a control group (iv prophylaxis alone).

The treatment group received two Collatamp®-G sponges in the wound immediately before closure as described above (Fig. 3). In the control group the wound was closed in a conventional way.

End point

The primary end point was any SWI within 2 months postoperatively. All analyses were made on an intention-to-treat basis, i.e. patients who died and those reoperated on for bleeding or other reasons during the follow-up period were included in the analysis.

Follow-up and data collection

During the postoperative stay in the surgical department, all reoperations and SWIs were recorded.

After discharge the patients were contacted by telephone 2 months postoperatively and were asked to answer a structured list of standardised questions. Those who could not be reached by phone were sent a letter with a questionnaire containing the same questions. Any reported symptom of impaired wound healing or possible wound infection resulted in a check-up of medical records from all postoperative contacts with medical services. Mortality data were double-checked against the national Swedish population register.

The interval from surgery to presentation of SWI was noted. The symptoms of SWI, as reported by the patient and/or documented in the patient's medical record, were recorded as including one or more of the following: secretion from the wound, redness of the

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wound, feeling of unstable sternal fixation, and presence of fever >38.5°C (during the SWI or within 3 days before diagnosis of SWI).

The highest plasma level of C-reactive protein (p-CRP) during the SWI or within 3 days before diagnosis of SWI was recorded when available.

Five samples for bacterial culture, of which at least two were tissue samples, were to be collected intraoperatively at reoperations for wound infection in cases handled at either of the two participating centres. In infected patients handled at referring hospitals, cultures were taken on clinical indications alone and according to local routines.

Classification of infections

The classification was made from all data available from the contact with the patient and collected medical records. Criteria for definition and classification of Surgical Site Infections according to the CDC system (1) were used with minor modifications (Table 6). Depths 1 and 2 were regarded as superficial infections and depths 3 and 4 as deep infections.

Table 6. Classification of infections

Depth	Localisation	Description	
1	Cutis	E.g. infected crusts)
2	Subcutis	Involving subcutaneous tissue but not reaching down to sternal fixation wires.	Superficial
3	Presternal	Infections reaching below the superficial fascia, involving sternal wires.	
4	Sternal bone or mediastinum	Unstable sternal fixation with signs of osteomyelitis or positive bacterial cultures from mediastinum or mediastinal abscess.	Deep

The infections were classified as "definite" or "probable". All probable and definite infections were considered as "infection" in the following calculations unless otherwise stated. To be classified as definite mediastinitis (depth 4), two of five cultures had to be positive with the same bacterial isolate.

Comment

Diagnosis and classification of surgical site infections are, despite classification systems, inevitably to some degree subjective. There were several cases where the clinical diagnosis of SWI (even regarding deep SWI) was uncertain even after extensive examinations and samplings. The SWIs were therefore classified as definite or probable and the latter group included all cases where infection could not be ruled out, irrespective of positive cultures, in an attempt not to underestimate the true incidence. The infections classified as superficial according to the CDC system were subdivided into two groups, since the most superficial ones (depth 1) could be considered less important clinically. Data regarding surgical revision of the wound because of SWI and data on antibiotic treatment were recorded. The indication for antibiotic treatment was not always evident and in a few cases antibiotics had been administered because of fever and elevation of p-CRP of uncertain cause. Antibiotic treatment was therefore defined as any antibiotic treatment during the first two months postoperatively.

Risk factors for sternal wound infection (III)

Eighteen pre-and intraoperative potential risk factors for SWI, including group affiliation (treatment/control), were tested by univariable analysis.

All factors in the univariable analysis with a P value of 0.2 or less were entered into the multivariable analysis. In addition, reoperation for bleeding was tested since it was significantly more common in the treatment group and also because it has been reported as a risk factor in the literature.

Use of an internal mammary artery (IMA) and type of operation are strongly correlated and the latter was therefore not entered in the multivariable analysis.

The risk factors that were found to be significant in the multivariable model were tested for statistical interaction with treatment group by adding the interactions one at a time to the multivariable model achieved with forward stepwise analysis.

Cost of a sternal wound infection and cost effectiveness of local gentamicin prophylaxis (III)

Model for calculating the cost of a sternal wound infection

This study was conducted from the perspective of the health care provider, excluding costs for production losses and patient costs.

Patients with SWI requiring surgical revision of the infected wound (59 patients: 38 and 21 in the control and treatment groups, respectively) and those who had been in-patients at a department for infectious diseases because of SWI (additionally 8 patients: 5 and 3, respectively) were considered the clinically most important groups. For all of these patients there were valid data in the medical records for the cost analysis and information on the following resource use was collected: Antibiotics given with SWI as the primary indication; the number of extra days spent in the ICU and in wards by reason of the wound infection; the number of surgical revisions of the wound under general or local anaesthesia; the use of diagnostic CT scan for diagnosis of the SWI; the number of out-patient visits to doctors and nurses concerning the SWI (Table 7). The number of days in the ICU and ward represent an assessment of the number of extra days caused by the SWI only, and not primarily by other concomitant complications.

All data were then converted to costs by applying a unit cost from the hospitals' internal economic systems. All costs were calculated in 2003 Swedish kronor (SEK) and then converted to euro (\mathfrak{E}) using the mean exchange rate during the year 2003 of $1\mathfrak{E}=9.12$ SEK (102) .The costs used in the calculations are shown in Table 7. The cost of the prophylaxis (two 10x10 cm Collatamp®-G) was $251\mathfrak{E}(2292$ SEK).

For a number of the less severe and late SWIs that had been treated by external medical services insufficient data were available for correct calculations of the cost.

For these 62 patients (44 in the control group and 18 in the treatment group) with clinically less severe infections the cost was "standardised" to the lowest possible realistic cost, i.e. one visit to a doctor and 10 days of treatment with oral isoxazolylpenicillin (flucloxacillin, 1 gram three times a day).

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Table 7. Resources and their allocated costs for the 129 cases with sternal wound infection

	Unit cost, euro	Number (%) of patients with any	Mean cost per SWI, euro
Surgical revision under general anaesthesia	2 288	53 (41.1)	2 359
Surgical revision under local anaesthesia	548	11 (8.5)	98
CT scan thorax	312	21 (16.3)	44
Days in the ICU	2 285	26 (20.1)	5 119
Days in a ward			
Cardiothoracic clinic	517	33 (25.6)	1 597
Infectious diseases clinic	728	41 (19.4)	2 461
Other clinic	334	34 (26.3)	1 431
Out-patient visit to doctor	221	52 (40.3)	395
Out-patient visit to nurse	57	17 (13.2)	130
Cost of antibiotics			847
TOTAL			14 481

CT = Computerised tomography; ICU = Intensive care unit

Cost effectiveness

The classification of the cases with SWI for the calculation of cost and of cost effectiveness is summarised in Figure 4. The cost of all SWIs in the control group was compared with the cost of all SWIs and of the prophylaxis in the treatment group to achieve a cost per avoided SWI.

Sensitivity analysis

Since the costs in the treatment and control groups may have been coincidentally and incorrectly influenced by a few costly SWIs in either group, the cost analysis was also performed with application of the same mean cost of all infections to both groups.

There was a higher incidence of reoperation for bleeding in the treatment group. A calculation including all reoperations for bleeding was therefore also conducted.

The influence of different costs of the prophylaxis as well as of different incidences of SWI was also explored.

Comment

The most obvious limitation to the method of cost estimation was the difficulty in assessing exactly to what extent the SWI contributed to the prolonged postoperative hospital stay or ICU stay in patients with a complicated postoperative course. However, the commonly applied approach in a case-control study involves problems associated with selection bias, which may be even larger.

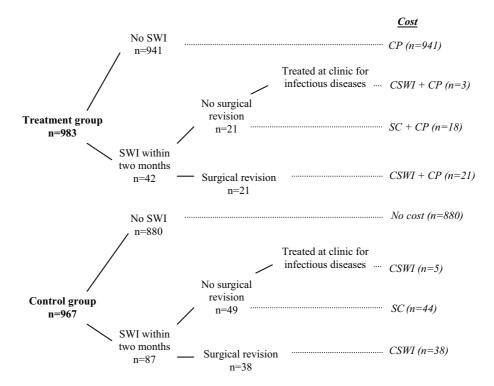


Figure 4. Sub-classification of the patients for calculation of costs in the treatment and control groups. SWI = Sternal wound infection

CSWI = Cost of sternal wound infection; CP = Cost of prophylaxis (251 euro); SC = Standardised cost (one out-patient visit to a doctor and oral flucloxacillin, one gram three times a day for ten days)

Microbiological findings in patients with and without local gentamicin prophylaxis (IV)

A total of 129 SWIs were analysed. All the results from the bacterial cultures were reviewed by a specialist in infectious diseases and/or clinical microbiology during the process of more detailed analysis of the microbiological findings and clinical symptoms (paper IV). In cases with multiple agents the probable primary causative agent was then purposely selected where possible and agents that were considered to be contaminants were excluded from further analysis.

The main groups of causative bacterial agents were compared from three main aspects: the cost of the treatment, the clinical presentation of the SWI and the effect of the gentamicin prophylaxis. The cost of the treatment of the SWI (calculated as described below) was used in this context as a measure of the general clinical "severity" of the infection.

Comment

The number and quality of bacterial samples varied. In cases with multiple agents the chronologically first isolated agent was selected and later findings were ignored in the analyses. However, in those few cases where more than one agent was primarily isolated the selection of the most probable causative agent involved an evaluation by the microbiologist.

Influence of additional sternal wires on deep sternal wound infection and on the efficacy of local gentamicin prophylaxis (V)

Subanalyses of the results of the trial had indicated discrepancies between the centres in the effect of the prophylaxis on DSWIs, with a weaker prophylactic effect at centre A. There was a small difference in the technique of sternal fixation between the centres. Immediately before the start of the LOGIP trial centre B had developed and evaluated a modification of the surgical technique with the aim of reducing wound infections. This implied a difference from the standard technique used at centre A in one main respect, namely that the sternum was "firmly closed with 7–8 single steel wires with special endeavour to stabilize the caudal part of corpus" (54). A more generous attitude towards using more than six wires was gradually also adopted at centre A. As a result a proportion of the patients at centre A received more than six wires, especially during the second year of the trial.

To assess the influence of the number of fixation wires, the number of sternal wires in patients operated on at centre A was counted by reviewing the first postoperative chest X-rays, which normally had been taken on the first morning postoperatively.

Comment

It is not known whether all surgeons at centre B complied with the policy regarding the number of wires in 100% of the cases, since postoperative X-rays were not available for examination at this centre, but for study purposes it was assumed that particular attention had been paid to securing rigid fixation of the caudal sternum in all patients at centre B. At centre A the number of wires may be less important per se, but use of additional wires may rather be an indication that the surgeon had paid more than usual attention to avoiding sternal instability.

There are two main limitations in the study design that are associated with retrospective analyses. The first limitation concerns the effect of the number of sternal wires where the patients were not randomised. Secondly, regarding the effect of local gentamicin excluding one subgroup of patients, this was a post hoc analysis that was not pre-defined in the protocol of the LOGIP trial.

Biochemical analyses

Dicloxacillin concentration (I)

The concentrations of dicloxacillin in blood and sternal wound fluid were measured by a bioassay with a PDM-agar plate (AB Biodisk, Solna, Sweden) that was flooded with an indicator strain, *S. aureus* 176. A standard curve was obtained by discs (PDM Standard Discs; AB Biodisk) with increasing concentrations of dicloxacillin. The concentrations in the patient samples (sera or wound fluid) that had been added to antibiotic-free discs could be interpreted according to the inhibition zone around this disc compared to the standard curve.

Gentamicin concentration (I)

The concentration of gentamicin was determined using a TDx fluorescence polarisation immunoassay (Abbott Laboratories, Abbott Park, IL, USA).

Comment

Dicloxacillin is strongly protein-bound in serum (95-98%) and only the free fraction is measured with the bioassay method. When the method is used for determination of dicloxacillin in the shifting composition of wound fluid with varying protein concentrations, the results are unavoidably inexact. However, since the free, non-protein-bound fraction is the active one and the one measured in this assay, the total concentration is less important. The concentration of dicloxacillin was determined in the serum and in the wound fluid, but not in tissue. It has been shown, however, that the serum levels of antibiotics correlate well with the tissue levels (67). The determinations of the gentamicin concentration should be less sensitive to protein concentrations since gentamicin is not highly protein-bound.

Microbiological analyses

Bacterial samples (II-IV)

The samples were aerobically and anaerobically cultured for at least 2 days on blood agar medium (Columbia II Agar 4.25% w/v; horse blood, defibrinised, SVA, Uppsala, Sweden, 6% v/v), with prolonged (\geq 5 days) incubation anaerobically, as well as in enrichment broth (fastidious anaerobe broth 29.7% w/v, Lab M, Lancashire, UK; and D+ glucose 10.0% w/v, J.T. Baker, Deventer, Holland) for 7 days. In infected patients handled at referring hospitals, cultures were collected on clinical indications only and the isolates were not regularly stored for further analysis.

Routine microbiological diagnostic procedures were used for identification of bacterial isolates. Susceptibility testing was performed on the staphylococcal isolates by the E test® (AB Biodisk, Solna, Sweden) and by the disc diffusion method (Oxoid, Hampshire, England) and the break points were all according to the recommendations of the Swedish Reference Group for Antibiotics (www.srga.org). A MIC value of ≤ 1 mg/L for methicillin, ≤ 1 mg/L for gentamicin/netilmicin and ≤ 4 mg/L for vancomycin was considered susceptible.

Comment:

Samples collected at surgical revision at centre A were frozen at -70° C and stored for further analyses.

Statistical methods (I-V)

Sample size

The sample size in the LOGIP trial was chosen so as to detect an approximate 50% reduction in the incidence of any SWI, and the incidence in the control group was assumed to be at least 4%. It was calculated that 1018 patients in each group would provide a power of 80% for distinguishing between infection rates of 4% and 1.9% in the two groups (two-sided type I error of 5%). To have 1000 patients in each group was therefore considered appropriate, since the incidence of 4% in the control group was assumed to be somewhat underestimated.

Materials and Methods

Risk factor analysis (III)

Risk factors for SWI were identified by univariable and multivariable logistic regression analysis.

A "P for trend" for each of the categorised variables (age, BMI and operation time) in the multivariable model was also obtained by entering them instead as continuous variables. To test the robustness of the multivariable model a second, forward stepwise multivariable analysis (likelihood ratio) was made. Also, a Hosmer-Lemeshow goodness-of-fit test was performed.

General statistical methods

Differences in proportions were expressed as the relative risk (RR) with 95% confidence intervals and two-sided P values were calculated with Pearson's Chi-square test or, if expected frequencies fell below 5, Fischer's exact test. For continuous variables the Mann-Whitney rank sum test was used. A P value of < 0.05 was considered significant. For the statistical analyses, Statistica® 7 (StatSoft Inc, Tulsa, OK, USA), SPSS® 13.0 (SPSS Inc, Chicago, IL, USA) software and Microsoft® Excel were used.

Results and discussion

Antibiotic concentration determinations

Dicloxacillin concentrations (I)

The concentrations in serum and wound fluid are shown in Table 8.

Table 8. Dicloxacillin concentrations, mg/L. Staphylococcus aureus and CoNS are defined as sensitive to oxacillin when the MIC is <1.0 mg/L.

	Time	No. of samples	Median	Min	Max
Blood	Sternal closure	97	59.4	9.5	215
Wound	Sternal closure	92	55.4	2	295
	4-9 h*	78	13.5	2.2	119
	11-16 h*	73	6.7	0.5	129
	17-22 h*	50	12.4	0.5	50.7

^{*}Time after sternal closure

The median levels were well above the MIC breakpoint for staphylococci (1.0 mg/L) in serum and wound fluid at sternal closure but there were large interindividual variations in concentrations. Little or no correlation was found between serum concentrations at the end of operation and body weight (r = -0.18) or preoperative serum creatinine (r = 0.11) (Fig. 5). The highest serum concentrations of dicloxacillin (> 100 mg/L) were all seen in patients above 60 years of age, but the correlation between age and concentration was poor (r = 0.14).

In the wound fluid the median concentrations were all above the MIC, but after 11-16 h as well as after 17-22 h the patient with the lowest concentration had a value of only 0.5 mg/L.

Comment

From these results the possibility cannot be excluded that there are suboptimal concentrations of dicloxacillin in the wound postoperatively in some patients. If this is so, whether or not it is of clinical significance remains to be clarified. The issue is complex since it has been recommended that further iv antibiotics should be avoided when the surgical wound has been closed, and therefore the need for antibiotics in the wound at all postoperatively may be questioned (1).

Our results do not provide a rationale for recommending individual dosage of dicloxacillin related to age, weight or serum creatinine.

Results and discussion

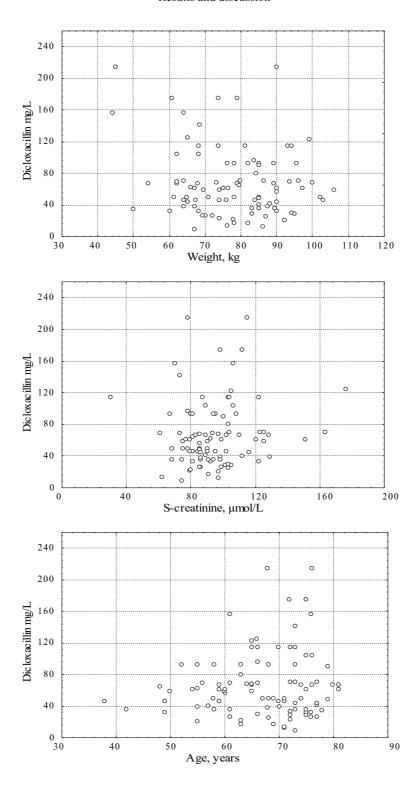


Figure 5. Correlations between serum-dicloxacillin at sternal closure and weight, s-creatinine and age.

Gentamicin concentrations (I)

The gentamicin concentrations in the serum in the 30 patients are shown in Figure 6. All patients had detectable levels of gentamicin in the serum. The nephrectomized patient showed different pharmacokinetics, which is shown as a separate line in Fig. 6. The wound fluid concentrations were much higher than those in serum, with a peak median of 304 mg/L (Fig. 6).

Comment

Besides the synergistic effect on bacteria sensitive to intravenously administered antibiotics, these high local gentamicin concentrations may be effective against agents that are often considered resistant to gentamicin as well as against those resistant to dicloxacillin, the clinically most important being CoNS. For reference iv gentamicin treatment aims at peak concentrations of about 4-12 mg/L.

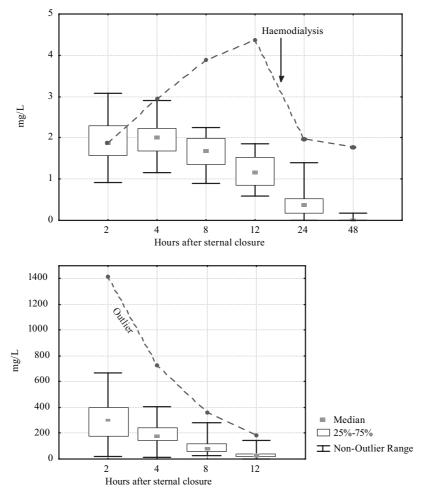


Figure 6. Gentamicin concentrations in serum (upper graph) and wound fluid (lower graph) after application of two collagen sponges (2 x 130 mg gentamicin) between the sternal halves. The outlier in the upper graph represents one patient without kidneys (not the same outlier as in the lower graph).

LOGIP trial

Effect of local gentamicin on sternal wound infections (II, IV)

Primary end point (II)

The total incidence of SWI (primary end point) was 9.0% in the control group and 4.3% in the treatment group (p<0.001). Significantly fewer patients in the treatment group received antibiotics or needed surgical revision of the sternal wound during the follow-up. Local gentamicin prophylaxis entailed a risk reduction at all depths and this was statistically significant for superficial infections (Table 9) and for deep infections in high-risk groups (DM, BMI > 25; Table 10).

Table 9. Primary end point and general outcome

Outcome	Control	Treatment	DD (05% CI)	D volve
Outcome	(n = 967) no. (%)	(n = 983) no. (%)	RR (95% CI)	P value
Primary end point	110: (70)	110: (70)		
All SWIs	87 (9.0)	42 (4.3)	0.47 (0.33 to 0.68)	< 0.001
Treatment				
Antibiotic treatment	174 (18.0)	114 (11.6)	0.64 (0.52 to 0.80)	< 0.001
Surgically treated SWI*	38 (3.9)	21 (2.1)	0.54 (0.32 to 0.92)	0.021
Sub-classifications				
Probable SWI	32 (3.3)	15 (1.5)	0.46 (0.25 to 0.84)	0.010
Definite SWI	55 (5.7)	27 (2.7)	0.48 (0.31 to 0.76)	0.001
All superficial SWIs	55 (5.7)	19 (1.9)	0.34 (0.20 to 0.57)	< 0.001
Depth 1	14 (1.4)	8 (0.8)	0.56 (0.24 to 1.33)	
Depth 2	41 (4.2)	11 (1.1)	0.26 (0.14 to 0.41)	
All deep SWIs	32 (3.3)	23 (2.3)	0.71 (0.42 to 1.20)	0.20
Depth 3	17 (1.8)	10 (1.0)	0.58 (0.27 to 1.26)	
Depth 4	15 (1.6)	13 (1.3)	0.85 (0.41 to 1.78)	
General outcome				
Hospital mortality	10 (1.0)	11 (1.1)	1.08 (0.46 to 2.54)	0.85
Total 60-day mortality	17 (1.8)	19 (1.9)	1.10 (0.57 to 2.10)	0.77
Early reoperation for bleeding	22 (2.3)	39 (4.0)	1.74 (1.04 to 2.91)	0.032
Postop haemodialysis†	10 (1.0)	10 (1.0)	0.98 (0.41 to 2.35)	0.97
Postop rise in serum creatinine, median, $\mu mol/L$	5.1	7.8		0.28
Mechanical ventilation for more than 48 h	25 (2.6)	31 (3.2)	1.22 (0.73 to 2.05)	0.45

^{*}Any surgical revision of the wound

[†]Patients on haemodialysis preoperatively not included

RR = relative risk; CI = confidence interval; SWI = sternal wound infection

Table 10. Incidence of sternal wound infections (SWI) in risk groups with diabetes mellitus or increased BMI

Risk factor(s)	Number (% of study population)	Depth of infection	SWI/total i Control	n group (%) Treatment	RR (95% CI)	P value
Diabetes*	354 (18.2)	Superficial	13/174 (7.47)	3/180 (1.67)	0.22 (0.06 to 0.78)	0.0086
		Deep	17/174 (9.77)	7/180 (3.89)	0.40 (0.17 to 0.94)	0.028
BMI>25†	1299 (66.6)	Superficial	42/651 (6.45)	14/648 (2.16)	0.33 (0.18 to 0.61)	< 0.001
		Deep	29/651 (4.45)	16/648 (2.47)	0.55 (0.30 to 1.01)	0.050
Diabetes and/or	1385 (71.0)	Superficial	46/687 (6.70)	14/698 (2.01)	0.43 (0.24 to 0.78)	< 0.001
BMI>25		Deep	30/687 (4.37)	17/698 (2.44)	0.56 (0.31 to 1.00)	0.047

^{*}Treated with insulin or oral medication

Microbiological agents and clinical presentation (IV)

Of the total 129 SWIs, only 24 (19%) (17 in the control group and 7 in the treatment group (P = 0.036)) were diagnosed before discharge from the cardiothoracic centre.

The microbial findings, their relative frequencies within the treatment and control groups and the effect of the prophylaxis are shown in Table 11 and Figure 7. Local gentamicin reduced the incidence of SWIs caused by all major clinically important bacterial species except *P. acnes*.

Table 11. The causative agents of the sternal wound infections and their relative frequency in each group. P values refer to difference in n (%) between treatment and control groups.

	Treatme	nt (n = 983)	Control	(n = 967)	
Bacterial agent	n (%)	% of infections in the treatment group	n (%)	% of infections in the control group	P value
S. aureus	7 (0.71)	16.7%	21 (2.17)	24.1%	0.007
CoNS	14 (1.42)	33.3%	35 (3.62)	40.2%	0.002
Gram-negative bacteria	1 (0.10)	2.4%	4 (0.41)	4.6%	0.21
P. acnes	7 (0.71)	16.7%	6 (0.62)	6.9%	0.80
Other, or multiple species	2 (0.20)	4.8%	6 (0.62)	6.9%	0.15
Negative or missing	11 (1.12)	26.2%	15 (1.55)	17.2%	0.40
Total	42 (4.27)	100.0%	87 (9.00)	100.0%	< 0.001

 $Treatment = local\ gentamic in\ prophylaxis;\ CoNS = coagulase-negative\ staphylococci$

[†]WHO definition of overweight

RR = relative risk; CI = confidence interval; BMI = body mass index (kg/m²), SWI = sternal wound infection

There was a significantly lower frequency of redness and a lower frequency of secretion from the wound and a trend towards a lower frequency of fever in the treatment group. However, there was no reduction in the occurrence of sternal instability (Fig 7).

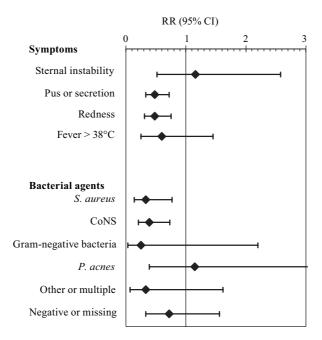


Figure 7. The effect of the local gentamicin prophylaxis on different symptoms of SWI and on different microbiological agents, expressed as the relative risk (RR) with 95% confidence intervals (CI).

Comment

A "per protocol" analysis was also made, excluding from the analysis patients who were reoperated on for bleeding (n=61), or reoperated on for other reasons (n=7), or who died within two months (n=36) (leaving 1850 patients, 927 and 923 in the control and treatment groups respectively). There were 62 (6.7%) v. 25 (2.7%) superficial sternal wound infections (SSWI) (P < 0.001), and 31 (3.3%) v. 19 (2.1%) DSWI (P = 0.088) in the control and treatment groups, respectively.

Although the study was not powered to detect differences in subgroups, the reduction in SSWI in the treatment group was significant and patients with established risk factors for infection (DM and/or increased BMI) showed a significant reduction in DSWI. The trend towards a greater reduction in SSWI compared with DSWI is difficult to interpret, as indicated by the wide confidence intervals in each subgroup. (The difference is not quite significant; a Chi-square test of a 2x2 table with the incidences of SSWI and DSWI gives an uncorrected P value of 0.053) From a clinical perspective, the significant difference in the incidence of infections that required surgical treatment is important.

Infections caused by *P. acnes* were the only ones which showed no absolute reduction in the treatment group. The possible association between *P. acnes* and sternal instability is further discussed later.

General outcome (II)

There were no significant differences in mortality, postoperative rise in creatinine or need for dialysis between the groups (Table 9). The total 60-day mortality of the 129 patients with SWI was 1.5% (two patients with deep SWI, both in the treatment group).

There were significantly more reoperations for bleeding in the treatment group (4.0% v. 2.3%).

Adverse reactions

No case of verified or suspected allergic or other adverse reaction to gentamicin or bovine collagen was identified.

Comment

The increased incidence of reoperation for bleeding in the treatment group remains unexplained. The medical records from the reoperation in the patients of the treatment group provided no obvious explanation, nor was any obvious, repeatedly observed or unusual source of the bleeding reported. Data retrieved from the clinical databases of the centres showed that 3.5% of the 792 patients not included in the study had had reoperations for bleeding. The incidence of reoperation for bleeding in the treatment group, 4%, was thus close to that seen among the patients not included in the study and in our routine practice. Furthermore, the difference in the incidence of reoperation for bleeding was only found at one of the participating centres (centre A), where the most remarkable finding was the exceptionally low incidence of reoperation for bleeding of only 1.4 % in the control group.

Risk factors for sternal wound infection (III)

Assignment to the control group, high BMI, DM, younger age, single or double IMA, LVEF below 35% and longer operation time were all independent risk factors for SWI in the multivariable analysis (Table 12). Longer operation time did not quite reach statistical significance in the multivariable model when entered as a categorised variable (P = 0.067) but P for trend was 0.016. The P values for trend for BMI and age were < 0.001 and 0.004 respectively. The Hosmer-Lemeshow goodness-of-fit test was non-significant (P = 0.141), which represents a well-fitting model.

In the univariable model emergency operation, steroid treatment, sex, and days of preoperative hospitalisation were not significant risk factors. Valve surgery was associated with a significantly lower incidence of SWI compared with CABG (OR = 0.49, 95% CI = 0.25 to 0.95) (not entered in the multivariable model).

Effect of prophylaxis in risk groups

There was a trend towards a larger relative risk reduction with the treatment in patients with DM and/or BMI > 25 (Fig. 8), although there were no statistically significant interactions between treatment group and any of these risk factors (P values for the statistical interactions treatment group*DM and for treatment group*BMI-class = 0.16 and 0.33, respectively).

Table 12. Multivariable logistic regression analysis of risk factors for SWI.

	OR	95% CI	P
Age, years			0.008 (0.004*)
<50	1.55	0.68 to 3.55	
50-59	2.09	1.30 to 3.37	
60-69	1.09	0.68 to 1.76	
70-79	ref		
>= 80	0.54	0.19 to 1.57	
Diabetes, insulin/drug treated	1.72	1.13 to 2.62	0.011
COPD	1.70	0.88 to 3.30	0.11
LVEF<35%	2.04	1.09 to 3.82	0.025
Unilateral IMA	1.83	1.12 to 2.99	0.016
Bilateral IMA	5.15	1.44 to 18.45	0.012
BMI			<0.001(<0.001*)
<=25	ref		
25-30	1.25	0.77 to 2.02	
>30	2.61	1.56 to 4.36	
Immunosuppression	2.02	0.55 to 7.41	0.29
Reoperation for bleeding	1.41	0.52 to 3.79	0.50
Operation time, hours			0.067 (0.016*)
2 hours or less	0.36	0.08 to 1.55	
2 to 3 hours	0.65	0.41 to 1.01	
3 to 4 hours	ref		
4 to 5 hours	0.76	0.43 to 1.33	
more than 5 hours	1.55	0.79 to 3.04	
Treatment group	0.44	0.30 to 0.65	< 0.001

^{*}P values within parentheses represent P for trend, i.e. the value achieved when the factor was entered as a continuous variable (not categorised) in the multivariable analysis.

Comment

The independent risk factors for SWI found in our study have been reported by others previously (6, 103-105). In contrast to most studies, however, early reoperation for bleeding and emergency operation were not significant risk factors in our study. The lower incidence of infections in older patients is also surprising. Use of one and of bilateral mammarian arteries were both significant risk factors. We did not use the technique of skeletonising when harvesting the IMA. It has been proposed that this technique may reduce the risk of postoperative SWI although, at present, there are no randomised controlled studies to prove this (106).

The trend towards a larger relative risk reduction in patients with DM or elevated BMI was noteworthy. There is no obvious biological explanation, however, why the prophylaxis should have less effect in slim non-diabetics, although the SWI rate is generally low in this group.

BMI = body mass index, kg/m2; COPD = chronic obstructive pulmonary disease;

IMA = internal mammary artery; LVEF = left ventricular ejection fraction

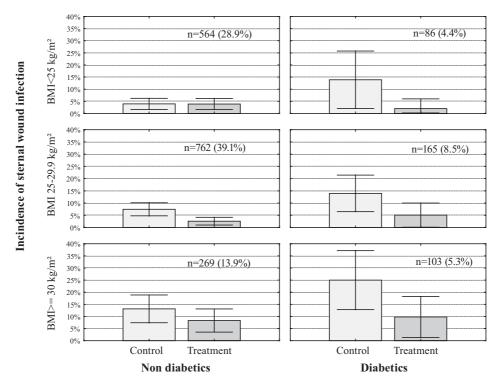


Figure 8. Incidence of sternal wound infection in the control and treatment groups stratified by diabetes (x axis) and BMI-class (y axis). Whiskers denote 95% confidence intervals. n = number of patients in each risk group (% of study population).

Cost of a sternal wound infection (III)

The mean cost of an SWI was approximately 14 480 \in (median 3 790 \in), with a range from 257 to 161 269 \in (Table 7).

A few of the SWIs accounted for a substantial part of the total cost (Fig. 9). The mean cost of one SWI was 12 419 ϵ in the control group and 18 752 ϵ in the treatment group (P = 0.31). The mean cost for the SWIs requiring surgical revision was 29 952 ϵ (26 586 ϵ and 36 041 ϵ in the control and treatment groups, respectively [P = 0.43]).

Comment

Our estimation of the cost of an SWI is on the same level as most other published figures (Table 1). Figure 9 highlights the large impact of a few very expensive infections. This is illustrated by the fact for example, that the cost (161 $269 \, \text{\ensuremath{\mathfrak{e}}}$) of the single most expensive SWI (belonging to the treatment group) could in itself explain the entire difference in mean costs between the groups.

Cost effectiveness of local gentamicin prophylaxis (III)

The cost effectiveness analysis showed that the addition of local collagen-gentamic nto intravenous antibiotic prophylaxis was dominant, i.e. resulted in both lower costs and fewer infections, in all groups of patients (Table 13).

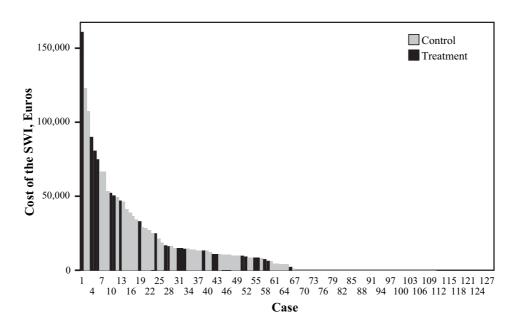


Figure 9. Total cost in euro of the treatment of each of the 129 SWIs

Table 13. Cost effectiveness in different risk groups.

	Group	n	No. of SWIs	Cost per patient, euro*	Cost- differ- ence, euro	Absolute risk reduc- tion	Cost per avoided SWI†	Max. cost of prophylaxis for which there is a positive net balance, euro
All patients	Control	967	87	1 117	-65	0.047	Dominant	316
	Treatment	983	42	1 052	-03	0.047		
Diabetes	Control Treatment	174 180	30 10	3 373 2 183	-1190	0.117	Dominant	1441
BMI>25	Control	651	71	1 506	240	0.062	Daminant	500
	Treatment	648	30	1 257	-249	0.063	Dominant	500
BMI>25	Control	687	76	1 516				
and/or diabetes	Treatment	700	31	1 232	-284	0.066	Dominant	535

^{*}Total cost of all the infections and of the prophylaxis in each group divided by the number of patients in each group

[†]Cost per avoided SWI is defined as the extra cost of the treatment (= cost difference) divided by the absolute risk reduction (mathematically identical to multiply by the numbers needed to treat). "Dominant" means there is no cost (= negative cost).

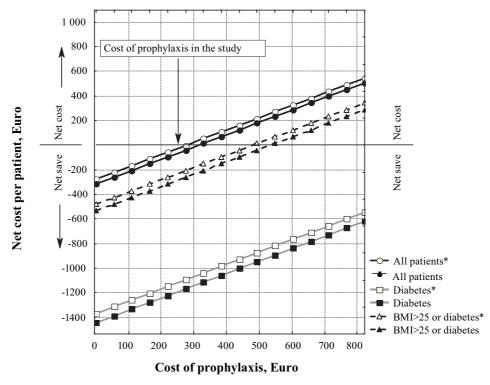


Figure 10. Net cost per operated patient in euro at different costs of the prophylaxis and the influence of reoperations for bleeding*. Values below zero mean a negative cost, i.e. a net save. *Lines with unfilled markers represent calculations including early reoperations for bleeding.

When the mean cost of all SWIs in both groups was applied instead in the calculations, thus assuming the cost of one SWI to be equal in the treatment and control groups, there was an even larger positive net balance up to a theoretical maximum cost of the prophylaxis of $\sim 680 \in$ when applied to all patients.

Figure 10 shows the influence of the cost of the prophylaxis on the net balance, applying the actual costs of the SWIs from Table 13. As shown, the inclusion of reoperations for bleeding in the analysis only marginally influenced the net balance.

Comment

Although the margin was small, there was a cost save even for the "worst case" cost calculations, i.e. when the prophylaxis was applied to all patients and assuming both a higher mean cost for the SWIs and an increased rate of reoperations for bleeding in the treatment group to be true (Fig. 10). The trend towards a larger *relative* risk reduction in patients with one of the major risk factors overweight (BMI > 25kg/m²) or DM has been mentioned in the risk factor section. Furthermore, the cost analysis showed that the mean cost of the infections was larger in these risk groups. It may therefore be more cost effective to restrict the prophylaxis to patients with either or both of these two risk factors.

Clinical presentation in relation to microbiological agent (IV)

Cost related to microbiological agent

Sternal wound infections caused by Gram-negative bacteria were associated with the highest mean cost for their treatment (41 828 $\[Delta]$). There were few less serious (and few late) infections in this group (Fig. 11). In some patients with SWI caused by *S. aureus*, the infections were costly, but in another, larger patient group with *S. aureus*, the infections were less serious and mostly late-onset. Cases caused by CoNS exhibited a similar heterogeneity, with a small proportion of very costly and severe SWIs. In fact, two out of three SWIs with a treatment cost exceeding $100\ 000\ \[Delta]$ were caused by CoNS (Fig. 11).

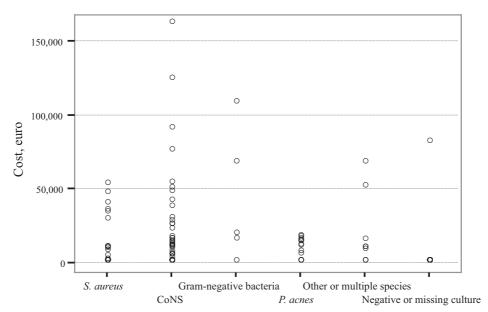


Figure 11. Cost of the treatment of each of the sternal wound infections. CoNS = coagulase-negative staphylococci.

Symptoms

Secretion from the wound was the most common symptom of SWI and was present in 84.5% of all cases and in 92% of all staphylococcal infections. Infections caused by *S. aureus* and Gram-negative bacteria were characterised by high p-CRP levels (median 275mg/L and 200 mg/L, respectively) and a high proportion of patients with fever (32% and 40% respectively). However, patients with SWIs caused by *S. aureus* had the lowest reported frequency of sternal instability (3.6%), while patients with infections caused by Gram-negative bacteria and *P. acnes* had the highest frequencies (40% and 38.5%, respectively). Patients with *P. acnes*, in contrast, showed comparatively low CRP levels (median 108 mg/L), despite early presentation of these infections. Details of the symptoms and characteristics of the SWIs are given in Table II in paper IV.

Time to presentation

The timing of the first manifestation of symptoms of SWI could be established in 108 of the 129 cases (in 79% and 86% of the treatment and control groups, respectively). The interval between surgery and onset of symptoms of SWI was shortest for infections caused by Gram-negative bacteria (median 5 days, range 2–20 days) and longest for those infections caused by *S. aureus* (median 20 days, range 5–62 days) (Fig. 12).

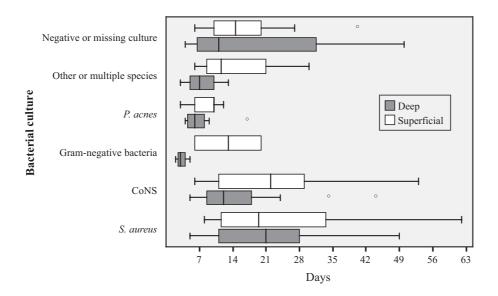


Figure 12. Time, in days, from the operation to the first symptoms of sternal wound infection, in relation to the depth of the infection. CoNS = coagulase-negative staphylococci.

Comment

Differences in clinical characteristics of the SWI depending on the causative microbial agent have been recognised by others (18, 19). In the current study SWIs caused by Gram-negative bacteria were clinically severe and characterised by early-onset, high CRP levels, a high proportion of cases with an unstable sternum, and the highest mean cost for their treatment. By contrast, staphylococcal infections usually presented later with local symptoms, with secretion from the wound as their predominant manifestation. Somewhat surprisingly, in our study *S. aureus* infections had a later onset of symptoms than did infections caused by CoNS, despite the fact that *S. aureus* is generally considered to be a more virulent agent. However, *S. aureus* infections constituted a heterogenic group, with a smaller proportion of early, more severe infections and a larger proportion of late, superficial infections. All microbiological agents, but particularly CoNS, showed a wide span in the general clinical severity of the SWIs, measured as the cost of their treatment. A high proportion of cases of sternal dehiscence and an early onset despite low CRP levels characterised the SWIs caused by *P. acnes* in our study. Thus the possibility of primary

characterised the SWIs caused by *P. acnes* in our study. Thus the possibility of primary mechanical sternal instability with secondary contamination with *P. acnes* should be considered, although clinical signs of wound infection were frequently present. Both CoNS and *P. acnes* belong to the normal skin flora and are agents with a low virulence

potential. Hence it is possible that host factors such as unstable sternal fixation play an important role in the pathogenesis of these infections, although CoNS – unlike *P. acnes* – caused a substantial proportion of clinically severe SWIs (measured as the cost of the treatment; Fig. 11). With the exception of one patient (in the control group), all patients with symptoms of sternal dehiscence that required refixation were classified as having an SWI. This low incidence of pure mechanical sternal instability was another fact motivating the post hoc analyses of the influence of the number of sternal fixation wires on the incidence of DSWI and on the effect of the prophylaxis (paper V).

Antibiotic susceptibility (IV)

Antibiotic susceptibility data were available for gentamicin in 47 (61%) out of 77 cases of SWIs caused by staphylococcal species; for methicillin, data were available in 62 out of 77 cases (81%). All tested *S. aureus* isolates were susceptible to both gentamicin and methicillin. There was a significant difference in the number of SWIs caused by gentamicin-susceptible CoNS (15 in the control group and five in the treatment group; P = 0.022) but not in the number caused by gentamicin-resistant CoNS (six and five SWIs in the treatment and control groups, respectively) (Fig. 13). There was a parallel difference in both methicillin-susceptible CoNS and MRSE, with seven MRSE infections in the treatment group and 16 in the control group (P = 0.05). Determination of MIC values for gentamicin by the E test® was performed for CoNS isolated from 12 patients who were reoperated on because of SWI. The MIC values ranged from <0.016 to 32 mg/L. No CoNS with highlevel gentamicin-resistance (HLGR), i.e. with a MIC value >256 mg/L, was found. All staphylococci that were tested against vancomycin (48 out of 77) were susceptible.

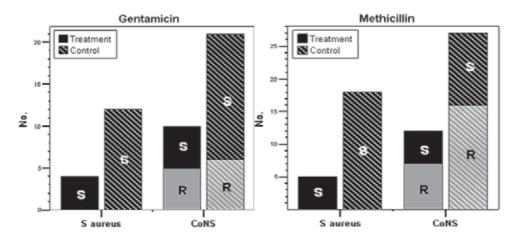


Figure 13. Patterns of antibiotic susceptibility to gentamic (left) and methicillin (right) in the treatment and control groups among the staphylococci isolated from the sternal wound infections CoNS = coagulase-negative staphylococci; R = resistant; S = susceptible.

Comment

There was a parallel reduction in SWI caused by methicillin-susceptible and methicillin-resistant CoNS strains. A similar reduction in MRSA infections would be of clinical importance, especially since the results from studies on routine iv vancomycin prophylaxis in cardiac surgery have been disappointing (94). However, there were no cases

of MRSA in our study. The prophylaxis neither increased nor significantly reduced the incidence of SWI caused by gentamicin-resistant CoNS. But it is too early to draw any conclusions on this issue on the basis of these results in view of the small number of cases, and this issue needs further exploration and surveillance in the future.

Influence of sternal fixation on occurrence of sternal wound infection (V)

There was an approximately 90% relative reduction in the incidence of DSWI in the XW group compared to the ST group, a difference which was highly significant, but there was no difference in SSWI (Table 14). The reduction in DSWI associated with extra-rigid fixation was evident only when the additional sternal wires were combined with local gentamicin; see below.

Table 14. The effect of additional sternal fixation wires. Incidence of sternal wound infections (SWIs) in the ST group (with six or fewer sternal wires) and XW group (with seven or more sternal wires) at centre A.

	XW group (n = 264)	ST group (n = 741)	Relative risk (95% CI)	P value
	n (%)	n (%)	0 XW better 1 ST better	r 2
All SWIs	13 (4.9)	59 (8.0)	1	0.13
SSWI	12 (4.5)	28 (3.8)	+	0.58
Depth 1 (skin)	3 (1.1)	10 (1.3)		1.00
Depth 2 (subcutis)	9 (3.4)	18 (2.4)		0.40
DSWI	1 (0.4)	31 (4.2)	 ♦	0.002
Depth 3 (sternum)	1 (0.4)	13 (1.7)		0.13
Depth 4 (mediastinum)	0 (0.0)	18 (2.4)		0.006

DSWI = deep sternal wound infection; SSWI = superficial sternal wound infection.

CI = confidence interval.

Comment

The use of seven or more sternal fixation wires (XW group) was associated with a marked reduction in DSWIs compared with the standard technique (ST group) with six or fewer wires. This supports the postulation that a meticulous surgical technique at sternal closure, with additional sutures for reinforcement of the caudal sternum, reduces the rate of DSWIs (53-55).

Since the difference in the incidence of reoperations for bleeding was only observed at centre A, and could theoretically have been related to less rigid sternal fixation, the incidence rates of reoperation in the ST group were compared with those in the rest of the patients. Again, the low incidence in the control group was the most striking finding; The incidence of reoperation among the patients in the ST group was 0.8% in the control group and 4.9% in the treatment group; among the rest of the patients 3.2% and 3.4%, respectively (unpublished). Since the sternal wires were counted after the reoperation – and could have been altered at the reoperation – the data are not conclusive.

Influence of sternal fixation on the efficacy of local gentamicin prophylaxis (V)

When the ST group was omitted from the patient population the total incidence of SWI was 2.8% in the treatment group and 9.0% in the control group (RR = 0.31 [95% CI = 0.18 to 0.53], P < 0.001). There was a parallel reduction in the incidence of SWI at all four depths (Fig. 14). The incidences of SSWI in the treatment and control groups were 1.8% and 5.9% (RR = 0.30 [95% CI = 0.15 to 0.59], P < 0.001) and the incidences of DSWI were 1.0% and 3.1% (RR = 0.32 [95% CI = 0.13 to 0.80], P = 0.01), respectively.

The incidence of SWI among the 741 patients in the excluded ST-group was also analysed. There was a significantly lower incidence of SSWI in the treatment group than in the control group with rates of 2.2% and 5.3%, respectively (RR = 0.40 [95% CI = 0.18 to 0.91], P = 0.02), whereas no significant difference was noted in DSWI (treatment group 4.6%, control group 3.7%) (RR = 1.24 [95% CI = 0.62 to 2.47], P = 0.55) in the treatment and control groups, respectively.

The XW group was too small (125 and 139 patients in the control and treatment groups, respectively) to allow for any meaningful analyses of the effect of the prophylaxis on DSWI within that group. There was one DSWI (0.8%, 95% $\rm CI = 0$ to 2.4%) in the control group and no DSWI in the treatment group.

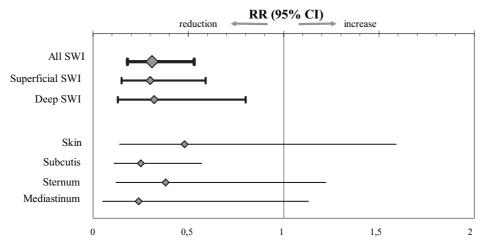


Figure 14. The effect of local gentamicin as prophylaxis on the incidence of sternal wound infections (SWIs) at the four different depths in 1 202 patients with extra-rigid distal sternal fixation. The figure shows the relative risk (RR) for SWI with 95% confidence intervals (CI).

Comment:

Local collagen-gentamicin as prophylaxis was associated with an approximately 70% relative reduction in the incidence of all depths of SWIs when the ST group was excluded from the total patient population. The reduction in DSWI as well as in SSWI was significant. Although the results were statistically highly significant, the limitations connected with post hoc analyses like this, commented on in the methods section, should be kept in mind.

Prophylactic effect of local gentamicin

Local application of collagen-gentamicin as prophylaxis was associated with a statistically significant 53 % relative reduction (4.7% absolute reduction) in the incidence of SWI after sternotomy in an unselected population of cardiac surgery patients when evaluated in an RCT. Although the difference did not reach statistical significance regarding DSWI in all patients, there was a significant reduction in DSWI in risk groups for SWI (BMI > 25 kg/m² and/or DM), in the incidence of surgically revised SWI, and in antibiotic treatment. Assignment to the control group was found to be an independent risk factor for SWI in the multivariable analysis. In patients with extra-rigid sternal fixation there was a significant, approximately 70% reduction in both SSWI and DSWI.

No significant impairment in postoperative renal function or other adverse effects of the treatment were noted.

The late manifestation of most SWIs and the 9% total incidence in the control group are notable (four out of five SWIs were detected after discharge from the cardiothoracic centre), but are in accordance with the findings in other studies with complete follow-up (3, 10, 107). A follow-up with recording of all SWIs up to discharge from the cardiothoracic unit not only underestimates the magnitude of the problem; it also carries a risk of providing a skewed picture, with an overrepresentation of Gram-negative infections. There was a reduction in SWIs caused by all major bacterial agents, and the significant reduction in SWIs caused by CoNS, the dominating agent, is paramount. One aim of applying local gentamicin was to find an ecologically appealing and at the same time effective alternative to vancomycin as prophylaxis for SWIs caused by MRSE and MRSA. The analyses of antibiotic resistance showed that local application of gentamicin resulted in a parallel reduction in SWI caused by methicillin-susceptible and methicillin-resistant CoNS strains. There were no MRSA infections in our study; however, surgical wound infections caused by MRSA, including SWI, are a well recognised and growing concern internationally. Although the possibility of aminoglycoside resistance among MRSA strains must be considered, recent reports from Europe and the USA indicate that many MRSA strains may be susceptible to gentamicin (108, 109). This technique therefore deserves to be evaluated as an alternative to prophylactic vancomycin in environments with a high prevalence of MRSA.

Prophylaxis and antibiotic concentrations

The routine iv dicloxacillin prophylaxis resulted in levels of dicloxacillin in the blood and wound fluid at sternal closure that were sufficiently high to prevent infections with methicillin susceptible staphylococci, although it cannot be excluded that mediastinal concentrations just below the MIC for staphylococci may have occurred in individual patients during the first 12 hours postoperatively. The application of collagen sponges containing a total amount of 260 mg of gentamicin between the sternal halves before sternal closure resulted in extremely high gentamicin concentrations in the wound fluid during the first 8-12 postoperative hours, but low serum levels. Not only did this lead to a reduction of SWIs caused by agents resistant to the iv prophylaxis (methicillin) but interestingly, the reduction was at least as important in SWIs caused by staphylococci susceptible to the administered iv prophylaxis.

The clinical relevance of the levels of antibiotics in the mediastinal fluid after closure of the cardiac surgical wound has not, to the author's knowledge, been studied previously. Obviously the presence of antibiotics in the wound postoperatively, and not only intraoperatively, did have a preventive effect on postoperative SWI in the LOGIP trial. However, the fact that it has not been possible to show any additional effect of prolonged iv prophylaxis (> 48 h) or any effect of adding iv gentamicin to routine iv cephalosporin indicates that it was the technique of local application of an antibiotic in the wound, rather than prolongation of the prophylaxis, that was the crucial factor (73, 79, 85, 86). Whether the mechanism was the extremely high early antibiotic concentrations, a synergism between gentamicin and cloxacillin, or possible late residual presence of gentamicin in the subcutaneous tissue or sternal bone is unknown.

Exclusion of all iv prophylaxis and relying on local antibiotic application alone would seem unwise in the light of the available documentation on the importance of adequate systemic antibiotic concentrations at skin incision (74). A combination of a short iv prophylaxis, that achieves high systemic antibiotic concentrations at skin incision and only as long as the surgical wound is open, followed by local application of an antibiotic in the wound, resulting in high local concentrations postoperatively, might be the most effective and ecologically attractive antibiotic prophylaxis.

Cost effectiveness

The prophylaxis technique was dominant in the cost effectiveness calculations, despite the fact that the mean cost of the treatment of an SWI was higher in the treatment group in the study, and despite the present cost of the prophylaxis. Cost calculations necessarily include some assumptions. The cost model used, however, deliberately underestimated the costs in many cases. Even so, there was a net save even in the "worst case" calculations. From an ethical point of view, it can be regarded as questionable not to apply a dominant therapy/intervention, since it both benefits the patient and saves money. Thus on the basis of our results routine use of the prophylaxis in all adult cardiac surgery patients could be recommended, although restriction to patients with DM and/or BMI>25kg/m² might be more cost effective. No data support any benefits of selective use in any other particular risk groups.

Issues of consideration

The effect on deep and superficial sternal wound infection

Local collagen-gentamicin prophylaxis was associated with a significant reduction in DSWI in risk patients, although the study was not powered to detect differences in subgroups. Nevertheless, there was a trend towards less reduction in the incidence of DSWI than in that of SSWI, although the collagen-gentamicin sponges were placed between the sternal halves. We hypothesized that this is where it is most important to achieve high antibiotic concentrations in order to prevent osteomyelitis.

The incidence of non-infected sternal dehiscence (one case compared with 55 cases of DSWI) was lower than is commonly reported (16). There was a striking reduction of DSWI in patients who had had the distal sternum reinforced with at least one extra wire and the impact of this extra wire on the strength of the fixation has support in the

literature (55). These results all suggest that in a substantial proportion of cases the mechanism underlying the development of DSWI was instability of sternal fixation rather than primary bacterial infection.

The finding that the weaker effect on DSWI was restricted to the ST group is therefore pertinent, and the application of collagen sponges between the sternal halves may require particular attention regarding the stability of the fixation to reach a full prophylactic effect on DSWI.

The association between CoNS and sternal instability has been well documented (16, 19, 110). Furthermore, of 13 SWIs caused by *P. acnes* in the trial, 12 occurred at centre A and of these 11 were in the ST group and only one in the XW group (unpublished). Both CoNS and *P. acnes* belong to the normal skin flora and are agents with a low virulence potential. Hence it is possible that host factors such as even a subtle instability in the sternal fixation play an important role in the pathogenesis of these infections. It is also conceivable that in earlier reports, *P. acnes* as well as CoNS – being parts of the resident micro-flora of the skin – may not have been recognised and reported as significant pathogens.

The increase in reoperation for bleeding

Further analyses have provided no explanation for this unexpected finding. The difference was evident only at centre A, where the most remarkable finding was the exceptionally *low* incidence of reoperation for bleeding of only 1.4 % in the *control* group.

According to the Swedish Cardiac Surgery Registry the incidence of reoperation for bleeding in all cardiac surgery operations in Sweden in 2004 was 4% (111). From this perspective, the incidence in the treatment group (4.0%) was not at all abnormal.

Future perspectives

Details of the technique

We used two collagen sponges corresponding to a total dose of 260 mg gentamicin (400 mg gentamicin sulphate). The optimal dose of local gentamicin is not known. Nor have the optimal release time and the optimal type of gentamicin compound been studied. Although the high bactericidal effect of gentamicin and the synergism with iv antibiotics may be important explanations for the marked reduction in SWI (99, 100), local application of alternative antibiotics could be evaluated as an option in environments with a high prevalence of gentamicin-resistant microbiological agents.

The application of collagen sponges between the sternal halves may, as mentioned, require particular attention concerning the surgical technique at sternal fixation, and awareness of this aspect when extrapolating the results of this trial to other types of collagen or other drug carriers with differing mechanical properties seems reasonable. In this respect the ideal carrier would probably be thin, easily compressible and rapidly absorbed.

Antibiotic resistance

The one most important issue that requires monitoring in the future concerns the possible development of gentamicin resistance. The reported incidence of gentamicin resistance among staphylococci varies, presumably as a reflection of aminoglycoside usage patterns (112-114). High incidence rates of aminoglycoside resistance have been reported especially

among CoNS and among hospital strains of MRSA (113). Plasmid-mediated HLGR among Gram-negative bacteria has also been reported (115). On the other hand, emergence of gentamicin-susceptible MRSA was reported from France during the 1990s (116), and a high rate of gentamicin susceptibility among community-acquired MRSA was recently reported from the United States (109).

Widespread use of gentamicin, or of any other antibiotic, will inevitably increase the risk for selection of resistant hospital strains over time. On the other hand, compared with iv treatment the short, single and very high peak in local gentamicin concentration does not favour selection of resistant strains. Furthermore, local gentamicin could lead to a reduction in the number of SWIs caused by CoNS isolates classified as gentamicin-resistant according to the break point ≤ 4 mg/L, since very high tissue concentrations are achieved by local application and since no CoNS with HLGR was found in this study among isolates obtained during reoperation.

It is emphasised that local prophylactic application of an antibiotic in a sternal wound before wound closure implies "internal" antibiotic treatment. Thus, the results of this work should not in any respect be interpreted as support for the use of topical treatment of open wounds or skin lesions with gentamicin or other antibiotics in general.

The reduction in the incidence of SWI achieved with the added prophylaxis decreases in itself the use of antibiotics for treatment of SWI and most importantly, local gentamicin provides the potential advantage of reducing the total exposure of the environment to vancomycin. Reduced susceptibility to glycopeptides among MRSA has recently been reported (89, 90), underscoring this need for alternatives to vancomycin as prophylaxis.

Applications outside cardiac surgery

The adverse impact of SSIs in terms of financial and clinical consequences among all kinds of surgical patients is indisputable. Major efforts and new methods to reduce the incidence are called for and may prove cost effective. Although the results of the present studies cannot be directly extrapolated to other than cardiac surgery patients, the addition of local collagen-gentamicin prophylaxis offers an alternative to iv prophylaxis alone, and deserves evaluation in RCTs in other fields of clean as well as contaminated surgery, also in environments with a high prevalence of methicillin-resistant staphylococci.

Conclusions

- Routine prophylaxis with dicloxacillin, 1 g, administered iv immediately before surgery and repeated after 2 hours of operation resulted in adequate levels of dicloxacillin in the blood and wound fluid at sternal closure
- Local application of collagen-gentamicin resulted in exceptionally high gentamicin levels in the wound fluid during the first 8-12 postoperative hours, but low serum levels
- Local collagen-gentamicin given in addition to routine iv prophylaxis resulted in
 - a statistically significant approximately 50% reduction in the incidence of SWI after sternotomy in an unselected cardiac surgery patient population
 - o a reduction in all depths of infection; this was statistically significant in superficial infections and, in risk groups (BMI > 25 kg/m² and/or DM), in deep infections
 - o a reduced incidence of SWIs caused by all major, clinically important microbiological agents except *P. acnes*
 - parallel reductions in SWIs caused by methicillin-susceptible and methicillin-resistant CoNS strains
- In patients with extra-rigid distal sternal fixation local collagen-gentamicin prophylaxis resulted in an approximately 70 % reduction in all depths of infection
- The application of collagen sponges between the sternal halves may require particular attention regarding the stability of the fixation
- The technique deserves to be evaluated as an alternative to prophylactic vancomycin in environments with a high prevalence of MRSA
- Four out of five SWIs were detected after discharge and reliable figures for the total rate of SWI after cardiac surgery and for the incidence of different microbiological agents can only be obtained by an active follow-up of all patients for at least two months postoperatively
- SWIs caused by Gram-negative bacteria were generally clinically severe and characterised by an early onset, whereas staphylococcal infections usually presented later with local symptoms
- Assignment to the control group, high BMI, DM, younger age, single or double IMA, LVEF lower than 35% and longer operation time were independent risk factors for SWI in the multivariable analysis
- The mean cost of an SWI for the health care provider was 14 481 €, with a range from 257 to 161 269 €
- A cost effectiveness analysis showed that the application of local collagen-gentamicin as prophylaxis was dominant, i.e. resulted in both lower costs and fewer infections
- Use of local collagen-gentamicin as prophylaxis can be recommended for all adult cardiac surgery patients, although restriction to patients with diabetes and/or BMI > 25 kg/m² might be more cost effective

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Nothing shocks me. I'm a scientist.

Harrison Ford, as Indiana Jones in *Indiana Jones and the Temple of Doom* (1984)

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