The endogenous pathway is a major route for deep sternal wound infection

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Abstract

Objective: Deep wound infections pose an increasing problem in cardiac surgery patients. Prospective infection monitoring is thus a means of identifying possible risk factors. Methods: Within a period of 5 months, a total of 376 adult patients, 260 men and 116 women, with a mean age of 62.6 years (range 18–88), underwent coronary bypass grafting \((n = 281)\) or other cardiac surgery procedures \((n = 95)\). Nasal cultures were taken preoperatively from every patient, as well as cultures of the wound during surgery and when dressings were changed thereafter. In addition, nasal cultures were taken from all the medical and nursing staff. To differentiate endogenous and exogenous infection pathways, DNA fingerprint analysis was performed. Results: A total of 38 patients \((10.1\%)\) developed a wound infection, in 14 patients this happened to be a deep wound infection, in 24 patients a superficial one. Five sternal wound infections were associated with mediastinitis \((1.3\%)\). The occurrence of a wound infection overall resulted in prolonged hospitalization \((29.4 \pm 24 \text{ days}, P = 0.001)\), but not in increased hospital mortality \((4.4\% \text{ vs. } 3.9\%)\). Obesity, diabetes mellitus and nasal carriage of \textit{Staphylococcus aureus} proved to be independent risk factors with an odds ratio of 2.07, 2.26 and 2.28, respectively. In all but one of the sternal colonizations with \textit{S. aureus}, DNA fingerprint analysis demonstrated an identical pattern of \textit{S. aureus} from the patient’s nose and sternum, indicating an endogenous infection pathway. Conclusions: The determination of the endogenous pathway for severe wound infection makes prevention possible by means of preoperative local \textit{S. aureus} eradication. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Deep sternal wound infection; Pulsed-field gel electrophoresis; DNA fingerprint analysis; Risk factors

1. Introduction

Surgical wound infections are a serious problem in open-heart surgery despite continuing efforts to improve pre-, intra- and post-operative conditions. Significant morbidity and mortality caused by infection is associated with a prolonged hospitalization and therefore with increasing cost of care [1,2]. According to different definitions of wound infection the incidence reported in the literature varies from 1.9\% to 15\%, especially if leg wound infections are included [3–5]. Therefore, numerous studies have been performed to analyze the risk factors associated with the development of surgical wound infection after open-heart surgery [6].

The most common pathogens causing wound infection after cardiac surgical procedures are \textit{Staphylococcus} species. The frequency of wound infections caused by \textit{Staphylococcus aureus} in cardiac surgery patients varies between 12\% and 36.4\% in proportion of the above mentioned overall rate of wound infections diagnosed [7,8].

In our institution and others, surgical wound infection poses an increasing problem with an aging and more morbid cardiac surgery patient population [9].

Thus, the determination of possible risk factors and infection pathways is of major interest at a time of dwindling health care resources.

We conducted a prospective study to investigate the risk factors for postoperative wound infection. Detecting colonization with \textit{S. aureus} was of primary concern due the importance of this organism in wound infection. Moreover, comparison of DNA fingerprint analysis of microorganisms recovered pre- and post-operatively may certify possible pathways for surgical wound infection and may point out the way to prevention.
2. Materials and methods

2.1. Clinical assessment

Within a period of 5 months 376 consecutive adult patients scheduled to undergo heart surgery were studied prospectively. Only patients scheduled for heart transplantation or emergent surgical procedures were excluded from the study. The institutional ethics committee approved the study, and informed consent was obtained from each patient.

All patients underwent a routine preoperative protocol including several laboratory and diagnostic investigations, and were hospitalized prior to the operation no longer than 4.3 ± 3.5 days. The operative site was routinely shaved the evening before surgery. This was done out of practical necessity inspite of the usual habit to do shaving right before the operation.

Surgeons involved in the study applied a standard operative protocol. Cardiopulmonary bypass was established with moderate to mild systemic hypothermia (26–30°C), flow rates of 2.0–2.4 l min⁻¹ m⁻² and a mean arterial pressure of 40–50 mmHg.

Sternal closure was achieved using six to eight single gauge wires, three of them through the manubrium and the remaining three to five wires through the body of the sternum. The wire sutures were adapted by manual twisting without using a special approximator. Muscles were adapted by single absorbable sutures. The subcutaneous tissue was tightened by single stitches of absorbable sutures, and for skin closure a continuous polyglycole suture was used.

Antibiotic prophylaxis was given every 8 h at the day of operation (Cefuroxim 1.5 g). In case of valvular replacement this was done the second postoperative day inclusively. Imipenem/Cilastin was substituted in case of allergy to cephalosporines. (Only those Staphylococcus aureus isolates recovered from the sternal and leg area were tested for antibiotic susceptibility, and only 1.7% of all Staphylococcus aureus isolates from the patients (and none from the personnel) were resistant to Cefuroxim).

If infection was suspected, empiric antibiotic therapy was initiated, depending on the most likely site of infection and according to the written guidelines from our infection control committee, which are based on our institution’s monitoring of antibiotic resistance. The initial antibiotic regimen was then altered according to the antimicrobial susceptibility pattern of the isolates.

2.2. Infection surveillance

Surgical site infections (SSI) were defined by the Infection control staff according the definitions of the Centers for Disease Control and Prevention [10]. Briefly, superficial SSI must involve only skin or subcutaneous tissue of the incision. In addition, superficial SSI must include at least one of the following: (1) presence of purulent drainage; (2) isolation of an organism from the incision; (3) presence of at least one of the following symptoms: tenderness, swelling, redness, or heat; and the incision is opened by the surgeon; or (4) diagnosis by the surgeon or attending physician.

Deep SSI must meet the following criteria: Infection occurs within 30 days after the operative procedure, infection involves deep soft tissue of the incision and at least one of the following is present: (1) purulent drainage from the deep incision; (2) deep incision that spontaneously dehisces or is deliberately opened by a surgeon when the patient is showing at least one of the following signs or symptoms: raised body temperature (> 38°C), localized pain, or tenderness, unless culture of the incision is negative; (3) abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathology or radiology examination; and (4) diagnosis of deep SSI is made by a surgeon or attending physician. Mediastinitis was defined as deep SSI including the mediastinal area.

2.3. Preoperative risk factors

Within a period of 5 months the following data (Table 1) were recorded prospectively: (1) age, (2) sex, (3) type of surgical procedure, (4) type of additional diseases, (5) risk factors for cardiac diseases, (6) status post myocardial infarction, (7) interval between hospital admission and surgical intervention, (8) type of antibiotic prophylaxis. Postoperative parameters were: (1) duration of ventilation; (2) clinical and chemical parameters of infection (blood pressure, heart rate, body temperature, urine output, leucocyte count, plasma level of c-reactive protein [CRP]); (3) duration of intensive care unit stay; (4) duration of wound drainage; (5) duration of pacemaker wires; (6) duration of venous catheterization (central venous catheter, Swan-Ganz-catheter, Shaldon catheter); and (7) duration of urine catheterization.

2.4. Microbiological screening

2.4.1. Patient-related samples

During hospitalization, numerous swabs (Table 2) were taken from each patient’s nose and skin (in all cases before operation).
skin disinfection procedures): (1) at the time of admission; (2) at the beginning of the operative procedure prior to skin incision; (3) at the end of the operation prior to sternal and leg wound closure; and (4) every time the wound dressing was changed, and on the day of discharge from our hospital.

2.4.2. Personnel-related samples

Additionally, swabs were taken from the nose of each member of the medical and nursing staff at the beginning and at the end of the study. This included nursing personnel working at peripheral and intensive care units as well as personnel working in operative areas, i.e. surgeons, surgical nurses, anesthesiologists, perfusionists. Microbiological differentiation and susceptibility testing were performed with standard diagnostic procedures.

2.5. Molecular typing

Following conventional standard identification and antibiotic resistance patterns, the S. aureus isolates were typed by DNA fingerprinting. For this purpose pulsed field gel electrophoresis (PFGE) was performed.

After isolation and overnight growth, S. aureus was centrifuged. The pellets were resuspended and mixed with 2% low-melt agarose and lysostaphin at 45°C. Agarose plugs were incubated with lysozyme, followed by digestion of bacterial deoxyribonucleic acid with SmaI. Pulsed field gel electrophoresis was performed using the CHEF DR III system (Bio-Rad, Munich, Germany). Run conditions were 6 V at an induced angle of 120 degrees from an initial switch time of 5 s to a final switch time of 35 s. The run was terminated after 20 h, and the gel was photographed after staining with ethidium bromide. Two samples were considered to be different, if they differed in more than two bands, and identical, if they differed in only one or two bands or in no bands at all.

2.6. Statistical analysis

Both univariate and multivariate techniques were used for statistical analysis. The univariate analysis of possible risk factors was performed using Contingency tables (chi-square); Fisher’s Exact Test was calculated for categorical variables, and Student’s (unpaired) t-test for continuous variables; a P-value <0.05 was considered significant. The odds ratio was calculated with the 95% confidence interval. Multivariate analysis was performed using stepwise logistic regression analysis using the SAS (Statistical Analysis Systems) program. All variables suggested by the univariate analysis (P < 0.05) were analyzed by forward selection (SAS, USA, version 6.10).

3. Results

3.1. Study population

Within the observation period of 5 months, a total of 376 adult patients (260 men, 116 women) with a mean age of 62.6 ± 10.7 years (range: 18–88 years) were enrolled in the prospective study. Two hundred and eighty one patients (74.7%) underwent coronary artery bypass grafting (CABG). 14 patients (3.7%) underwent valve replacement in addition to CABG. 58 patients (15.4%) underwent valve replacement and 23 patients (6.1%) underwent miscellaneous cardiac surgery procedures. The overall hospital mortality of the study population was 3.9% (15 patients). A total of 241 individuals were included in the screening of nasal colonization in personnel at the beginning and the end of the study.

3.2. Surgical site infections

According to the CDC definitions of nosocomial SSI [10], 38 patients (10.1%) developed wound infections during the postoperative period, 24 superficial (6.4%) and 14 (3.7%) deep ones. A total of 25 patients (6.6%) developed sternal wound infections, 16 of them (4.3%) superficial and nine (2.4%) deep ones, including five cases (1.3%) of purulent mediastinitis that necessitated operative revision.

Eight patients (2.1%) manifested superficial leg infections and five patients (1.3%) deep ones. Five patients (1.3%) showed both sternal and leg wound infections. An overview of all infections is shown in (Fig. 1). As compared with the group of patients who did not develop postoperative wound infections, these patients did not differ significantly in sex, age, and type of surgery.

The occurrence of wound infections prolonged the duration of hospitalization (29.4 ± 24 vs. 11.9 ± 6.9 days; P = 0.001), but did not increase hospital mortality (4.4% vs. 3.9%; P = 0.1). These patients showed significantly elevated levels of CRP, elevated body temperature, and prolonged duration of pacemaker leads (P = 0.001). The
results of the univariate analysis of preoperative and postoperative risk factors are depicted in Table 3.

### 3.3. Colonization with S. aureus

Throughout the study period, 4755 swabs were taken from 376 patients. Overall 257 strains of *S. aureus* were isolated. On admission 106 (23.2%) patients showed nasal colonization with *S. aureus* and 23 patients (6.1%) had cutaneous colonization with *S. aureus*. Of the latter, 18 patients (4.8%) had simultaneous nasal bacterial colonization with *S. aureus*. Only five patients (1.3%) had just a cutaneous colonization.

At the beginning of the operative procedure, 23 *S. aureus* strains could be isolated from the swabs taken from the skin of the chest. At the end of the operation, cultures were taken from the sternum and leg wounds immediately before closure, and only three patients showed colonization with *S. aureus* at this time. According to the preoperative investigation 19 out of these 26 patients were nasal carriers of *S. aureus*. Throughout the postoperative period, 14 patients showed sternal colonization with *S. aureus* and 13 patients colonization of the wound of the leg.

### 3.4. *S. aureus* isolates from patient’s infection sites

*S. aureus* could be isolated from three patients with superficial leg infection, one patient with deep leg infection, and five patients with superficial sternal wound infection. Moreover, in seven out of nine cases of deep sternal wound infection, including the five cases with mediastinitis, *S. aureus* could be cultured from the purulent discharge. This corresponded to an infection rate of 26%, i.e. a statistically significant increase ($P < 0.05$) in the risk of postoperative wound infection in comparison to the rate of 7.7% in patients with a normal nasal flora.

Other organisms recovered from sternal or leg wounds during the surveillance period included coagulase-negative *Staphylococci* (13 isolates), *Pseudomonas aeruginosa* (six isolates), *Enterobacter* species, *Escherichia coli*, *Klebsiella oxytoca* (three isolates each per species), *Enterococcus* species, *Serratia marcescens*, and *Acinetobacter* species (one isolate per species). In nine patients, more than one species could be cultured from the specimens taken.

### 3.5. Isolates from personnel samples

Out of 241 individuals 59 were nasally colonized with *S. aureus* (incidence during the first examination 21%, during the second one 28%). The elevated number of colonizations in physicians (36%) in comparison to nurses (22.4%) is statistically not significant, as well as the different colonization between personnel in intensive care units and other wards.

### Table 3

Univariate analysis of several items to be determined as risk factors

<table>
<thead>
<tr>
<th>Item</th>
<th>Patients without infection ($n = 338$)</th>
<th>Patients with infection ($n = 38$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis of preoperative risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>58.9</td>
<td>81.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Diab. mellitus (%)</td>
<td>26.3</td>
<td>44.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>53.7</td>
<td>73.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Nasal carriage of <em>S. aureus</em> (%)</td>
<td>26.3</td>
<td>44.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Status post myocardial Infection</td>
<td>39.3</td>
<td>60.5</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Univariate analysis of risk factors associated with wound infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temp.$\geq$36.5°C (%)</td>
<td>40.2</td>
<td>65.7</td>
<td>0.004</td>
</tr>
<tr>
<td>CRP.$\geq$1 mg/dL (%)</td>
<td>17.7</td>
<td>42.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Period of pacemaker leads (days)</td>
<td>10.6 ± 6.5</td>
<td>21.7 ± 22.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Period of venous catheterization (days)</td>
<td>7.4 ± 3.7</td>
<td>13.7 ± 7.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Period of hospitalization (days)</td>
<td>11.9 ± 6.9</td>
<td>29.3 ± 24.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 1. Distribution of surgical wound infection in patients studied prospectively.
3.6. Genotype pattern

In all but one case of sternal colonization with *S. aureus*, identical DNA fingerprint analysis of *S. aureus* from patient’s nose and sternum could be demonstrated. In four out of five patients who developed mediastinitis during their postoperative course, the DNA fingerprint analysis again revealed a genotypically identical pattern of *S. aureus* from the patient’s nose and purulent mediastinal discharge (Fig. 2).

In one case of deep sternal wound infection, two cases of deep leg wound infection, and in seven patients with colonization of the wound without infection, *S. aureus* DNA fingerprint analysis demonstrated an exogenous pathway of infection and colonization. The isolates of these patients were compared with the isolates obtained from the staff at our hospital. In two cases, the isolates from a nurse on the regular ward and the isolates of the purulent drainage from two patients with deep leg infection showed identical DNA fingerprint analysis, demonstrating an exogenous pathway of these two SSI. For the other cases the sequence of colonization could also be interpreted by endogenous origin with secondary spread to nurses and other personnel. However, the remaining strains were not related to the *S. aureus* isolated from the personnel.

3.7. Statistical analysis of risk factors

Table 4 shows the crude odds ratios with 95% confidence intervals for the most important risk factors. Univariate analysis indicated arterial hypertension, status post myocardial infarction, obesity, diabetes mellitus, and nasal carriage of *S. aureus* as risk factors for developing a wound infection.

According to multivariate analysis, obesity, diabetes mellitus, and nasal carriage of *S. aureus* proved to be independent risk factors for the development of wound infections throughout the postoperative period after open-heart surgery.

4. Discussion

In accordance with other authors the study shows, that sternal wound infection remains a serious problem in cardiothoracic surgery and is associated with an increasing morbidity and mortality. In our prospectively evaluated series of patients the overall occurrence of 10.1% of wound infections seems to be high, but relates to the strict CDC criteria of SSI, which have been used by a few other groups who reported similar results [11–13].

According to our standardized postoperative regime, pacemaker leads and wound drains were left in place for a rather long period of time. Statistical analysis showed that wound infections were associated with a significantly longer placement of pacemaker reads, leg drains, and indwelling catheters. Statistical analysis, however, only describes and does not determine the cause of infection, possible only by employing molecular methods. Therefore, this study was performed prospectively in order to determine the cause of severe SSI.

In the past, numerous retrospectively performed studies have indicated a large number of possible risk factors which contribute to the onset of major SSI; these include sex, the presence of pulmonary disease, pneumonia, obesity, re-exploration, the use of an intraaortic balloon pump, diabetes mellitus, and bilateral internal mammary artery bypass grafting [4,14]. The latter depends mainly on the presence of additional diseases such as obesity or insulin-dependent diabetes mellitus [15,1]. In addition, Ottino et al. noted the


<table>
<thead>
<tr>
<th>Parameters</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.26</td>
<td>0.03</td>
</tr>
<tr>
<td>Nasal carriage of <em>S. aureus</em></td>
<td>2.28</td>
<td>0.03</td>
</tr>
</tbody>
</table>
association between hospital environment and the interval between admission and operation, and the development of major sternal wound infection [6].

However, at least some disadvantages are inherent to retrospectively performed studies, and it is postulated that the performance of a prospective study appears to be a prerequisite in order to determine risk factors for SSI [11].

Considering prospective studies the Parisian Mediastinitis Study Group determined obesity, bilateral internal thoracic artery grafting and postoperative inotropic support as independent risk factors [16]. Breyer et al. proved the association of prolonged ventilation and female sex with an increased risk of major wound infections [11].

Recently, Kluymans et al. [13] for adult patients and Ruef et al. [17] for a cluster of pediatric patients showed a linkage between nasal carriage of S. aureus and an increasing rate of postoperative wound infection. Likewise, Luzar et al. [18] reported in a prospectively performed study that nasal colonization with S. aureus increased incessantly the risk of catheter exit site infection in patients on continuous ambulatory peritoneal dialysis.

In our prospective study group, univariate analysis indicated arterial hypertension, status post myocardial infarction, obesity, diabetes mellitus, and nasal carriage of S. aureus to be risk factors for the development of wound infection during the postoperative course. According to multivariate analysis, obesity, diabetes mellitus, and nasal carriage of S. aureus remained as significant risk factors for the onset of major wound infection.

Nasal carriage of S. aureus has been well known as a risk factor for the development of surgical wound infection for 40 years. As early as 1959, Williams et al. reported an increased risk of wound infection in patients carrying this microbiological agent in the nose preoperatively [19]. Also in 1959, Weinstein et al. [20] analyzed nasal pathogens and postoperative infections in patients undergoing major surgery. Patients with a preoperative colonization had an infection rate of 37 vs. 11% in 82 patients with negative nasal cultures.

These findings were confirmed by Kluytmans et al., reporting on ten cases of genotypically identical strains of S. aureus recovered pre- and postoperatively and compared by phage typing [13]. More recently, Corbella et al. demonstrated the identity of nasal isolates and clinically recovered strains of S. aureus [21]. Ruef et al. were able to prove identical genotypes of S. aureus recovered from the nose and the sternal wound, too and speculated whether nasal colonization was present before the onset of infection or whether this resulted out of secondary spread from an infected site. Up to now, only Weinstein, Kluytmans and the Parisian Mediastinitis Study Group has conclusively demonstrated nasal carriage of S. aureus as a risk factor for wound infection in cardiothoracic surgery patients [13,16,20].

In our study group, 106 patients (28.1%) showed colonization of the nose prior to the operation and 17 (16%) of these developed SSI including eight patients in whom S. aureus was recovered from the purulent drainage. In contrast, 270 patients (71.9%) had normal flora in the nose, and only 7.7% of these patients developed a SSI during the postoperative course. Our results clearly indicate that there is a significantly elevated risk of developing a major wound infection for patients with preexisting colonization (P = 0.03). The incidence of nasal colonization with S. aureus in the normal population is reported to range from 10 to 15% in current literature [22]. As we took the nose swabs at patient’s admittance to hospital, we could exclude long-term preoperative hospitalization being responsible for this increased rate of nasal colonization, but the increased incidence remained unclarified.

The most striking result of our study was the fact that in four out of five patients suffering from mediastinitis, DNA fingerprint analysis using PFGE revealed the genotype of S. aureus isolates recovered from the patient’s sternum and nose after admittance to hospital to be identical. In contrast, in two cases we could determine identical restriction patterns of S. aureus from the patient’s infection site and the nose of a nurse, indicating that transmission from the personnel did in fact occur rarely. Our study is the only one with a prospective design to employ DNA fingerprinting of S. aureus isolates for tracing the source of infection in cardiac surgery patients so far. According to the current literature, identical restriction patterns denote the same band of pattern or up to two different bands in the patterns of different isolates after complete restriction enzyme digestion of bacterial DNA and subsequent PFGE. Isolates of the same species with more than two different bands are different strains [23]. The results obtained from the PFGE that showed identical patterns for the strains recovered from the patient’s nose and sternal wound clearly indicate an endogenous pathway for these infections. Previous investigations had indicated this pathogenesis, but were retrospective case control studies [13,16] a method with severe limitations [24]. DNA fingerprinting, i.e. digestion of the DNA of S. aureus subsequent PFGE, and visual comparison of the band of patterns obtained, was chosen because it has been shown to be superior to phage typing in demonstrating identification of microorganisms of the same species. This is crucial in tracing the exact source of infection from different sites of the same patient [23].

Kluytmans et al. studied the value of preoperative elimination of nasal carriage of S. aureus using mupirocin as nasal ointment. The results of this study clearly indicate that preoperative elimination of nasal carriage does indeed reduce the rate of SSI significantly [25], and therefore reduces the costs of postoperative care. The detection of S. aureus nasal carriers on admission may be particularly useful in identifying those patients who are at high risk for developing staphylococcal infections during the stay at the hospital.

In conclusion, after open-heart surgery the occurrence of major wound infection remains an ongoing problem for patients and the whole hospital environment [26].
According to our results and in order to avoid infection during the postoperative course, special attention should be paid to patients with obesity, diabetes mellitus, or nasal carriage of *S. aureus*. The determination of an endogenous infection pathway makes it possible to eradicate this source of infection prior to elective surgery by detecting it early and using local antibiotic administration for several days to reduce the risk of SSI.

References


