Surgical site infections in vascular surgery

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*Surgical site infections in vascular
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SURGICAL SITE INFECTIONS IN VASCULAR SURGERY

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht, op gezag van de rector Magnificus, Prof. dr. Rianne M. Letschert volgens het besluit van het College van Decanen, in het openbaar te verdedigen op

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Chapter 1

INTRODUCTION

INTRODUCTION

The main portion of vascular surgery consists of treating either occlusive or aneurysmal vascular disease. Arteries can become afflicted, causing them to narrow, sometimes to complete occlusion, or dilate. Occlusive arterial disease is mainly caused by atherosclerosis; a hardening of the intimal layer through build-up of plaques ^{1,2}. Main risk factors for atherosclerosis include dyslipoproteinaemia, diabetes, cigarette smoking and hypertension ². The pathophysiological basis of aneurysmal disease has a different basis that is not yet entirely understood, but its hallmarks include inflammation, smooth muscle cell apoptosis and degradation of the extracellular matrix which lead to reduced elasticity of the vascular wall ³⁻⁵.

Open and endovascular surgery are among the most important treatment modalities for both diseases. A major post-operative complication, which can cause substantial morbidity and mortality, is surgical site infection (SSI). Therefore, it is essential to gain insight in the development and possible prevention of surgical site infection. A significant part of this thesis will cover these aspects, though first I will elaborate on the two above-mentioned diseases.

Peripheral arterial occlusive disease

Peripheral arterial occlusive disease (PAD) affects a sizeable proportion of the adult population; its prevalence rising with age. The total disease prevalence ranges between 3% and 10%, increasing up to 15% to 20% in persons over 70 years of age ^{6,7}. Clinical presentation depends on the severity of PAD, though usually starts with intermittent claudication (IC). IC is characterized by muscle pain or discomfort in the lower limb provoked by exercise and relieved by rest within 10 minutes ⁶. A more severe form of PAD is critical limb ischemia (CLI), characterized by ischemic rest pain, which may be accompanied by ulceration or gangrene. Whereas the clinical course of IC is stable, with major amputation rates between 1% and 3% over a 5-year period, between 16% and 40% of CLI patients will lose their leg within 1 year without appropriate surgical therapy ^{6,8}. In literature, the Rutherford classification is used to describe the various stages of PAD ⁹. This scales from mild to severe claudication (Rutherford 1-3) to ischemic rest pain (Rutherford 4) and minor to major tissue loss (Rutherford 5-6) ^{9,10}.

Management of PAD

The primary treatment for IC (Rutherford 1-3) consists of risk factor modification (by means of smoking cessation, blood pressure management, cholesterol management and antiplatelet therapy) and supervised exercise therapy (SET) to improve symptoms ^{11,12}. Should SET fail to increase walking distance or reduce complaints, endovascular treatment is the therapy of choice for most claudicants, reserving open bypass surgery for individuals with significant functional disability (Rutherford 3) ^{1,6}.

In case of CLI (Rutherford 4-6), the scope of therapy switches from relieving symptoms to saving the affected limb, which requires swift revascularization ^{1,6}. The preferred treatment depends on the site and length of the lesion, with longer lesions being less optimal for endovascular therapy. In lesions where both modalities are possible, open and endovascular revascularization are broadly similar in outcome with lower costs for endovascular treatment and slightly worse short-term but better long-term outcome for surgical treatment ¹³. However, some elderly patients are too frail for either way of revascularization. Recent research has shown that for these patients, conservative therapy seems to be an acceptable treatment option with gained physical health at 6 months ¹⁴.

In open bypass revascularization, the graft of choice depends on the surgical site. For supra-inguinal (aortoiliac) lesions a polyethylene terephthalate (Dacron) graft is preferred. Due to better immediate and long-term patency, autologous saphenous vein grafting is preferred in peripheral lower limb bypasses. Only if autologous venous grafting is impossible, due to unfavorable morphology or absence of the greater saphenous vein, extended polytetrafluoroethylene (ePTFE) should be used ¹⁵⁻²⁰. It is important to note that SSI developing in patients treated with prosthetic grafts are especially difficult to treat and are associated with high morbidity and mortality ^{21,22}.

Aortic aneurysmal disease

Abdominal aortic aneurysm (AAA) is defined as a minimum diameter of the abdominal aorta that is greater than 30mm ²³. Its prevalence ranges between 0-1.3% at age 45 and 5.2-12.5% for patients over 75, with the majority of cases being without symptoms ²⁴. The natural history of AAA is characterized by gradual expansion of the aortic diameter and the accumulation of intraluminal thrombus. The most widely recognized complication of AAA is rupture, with overall mortality rates estimated as high as 90%, though recent studies show contemporary in-hospital mortality is under 30% ²⁵⁻²⁹. To prevent aortic rupture, the general agreement is that reconstructive surgery should be considered at an aortic diameter greater than 50mm for women or 55mm for men ³⁰⁻³⁴.

Currently, there are two treatment options, either open or endovascular reconstructive surgery. Open surgical repair, by aortic tube graft or aortoiliac bypass graft, has long been the standard, until the rise of endovascular aortic repair (EVAR) since its first use in 1987 ^{35,36}. The benefit of EVAR is found in lower perioperative mortality, a survival benefit which lasts until 1 to 3 years after surgery ³⁷⁻⁴⁰. A Dutch randomized controlled trial (DREAM trial) showed, if possible, endovascular repair has lower rates of perioperative mortality and complications and significant reduction in the rates of systemic complications ⁴¹. As with peripheral bypass surgery, open aortic graft surgery is prone to surgical site infection and graft infection ⁴². These are severe infections leading to high morbidity and potential death.

The role of SSI in endovascular aortic repair is not yet known and is one of the focuses of this thesis.

Surgical site infections in vascular surgery

Postoperative surgical site infections are a substantial cause of morbidity and mortality among vascular surgery patients. SSI is defined as the presence of heat, redness, swelling or pain around the wound within 30 days after the initial procedure and/or the presence of a positive culture, drainage of the wound or pus after a diagnostic puncture ⁴³. These infections may be superficial or deep incisional infections, or infections involving organs or pre-existing body spaces ⁴⁴. The incidence of SSI ranges from 1-2% after open or endovascular aortic interventions to 10-20% after lower limb bypass surgery ⁴⁵. Deep SSI is associated with graft infection, which can lead to sepsis, secondary aortic rupture, and death. Surgical intervention is often required, with reported 30-day mortality as high as 28% ^{21,22,46}. Vascular surgery patients are at high risk for SSI, due to frequent use of foreign material implants, use of groin incisions ^{47,48}, frequent re-interventions ⁴⁹ and shared risk factors for PAD and SSI ⁴⁴.

In most SSIs, the responsible micro-organisms originate from the patient's endogenous flora ⁴⁴. As typical commensals of the skin ^{50,51}, *Staphylococcus aureus* and coagulase-negative staphylococci are most associated with SSI in vascular surgery ⁴⁴. Both bacteria are known to produce biofilms on surgical implants, making them extremely resistant to antibiotic treatment ^{52,53}. Another complicating factor is the globally growing resistance of these pathogens to antibiotics. Especially methicillin-resistant *S. aureus* (MRSA) is a growing concern in the treatment of SSI, with methicillin-resistant strains comprising from 1-5% (Northern Europe) to >50% (Southern Europe, parts of Asia and the Americas) of all *S. aureus* isolates, varying between countries ^{54,55}.

Costs of complications

While a considerable part of SSIs can be prevented by relatively simple measures, recent research has shown that despite implementing a bundle of care providing a 51% reduction in vascular surgery SSI, 8.3% of patients still developed a SSI ⁵⁶. Besides increased morbidity and mortality, SSIs pose a significant burden to healthcare costs due to prolonged hospitalization, diagnostic tests, medical treatment and even reoperation. SSI has been shown to increase costs by 1.3 to 2.7 times compared to patients who do not develop a SSI ⁵⁷⁻⁶⁰. The increased costs depend on the depth of SSI, ranging from US\$726 to US\$20,000 added cost case ^{58,61-63}. The majority of studies, however, do not take into account the wider impact of SSI on society. For example, economic costs also arise from patients requiring longer absence from work, resulting in lost income and reduced work productivity ^{64,65}. Moreover, due to a growing trend of shortened postoperative hospital stay, a higher ratio of SSI develops after discharge ^{66,67}, which is associated with higher costs related to community healthcare visits

^{68,69}. Overall, this could result in US\$1-US\$10 billion in direct and indirect SSI-related health costs each year ^{46,70}.

AIMS AND THESIS OUTLINE

The aim of this thesis is to evaluate the occurrence, prevention and risk factors of surgical site infections after vascular surgery.

Prevention of surgical site infections in vascular surgery

Staphylococcus aureus nasal carriage is associated with an increased risk of developing a SSI in multiple populations ^{71–74}. Preoperative screening and treatment of nasal *S. aureus* carriers is a cost-effective method of reducing the risk of SSI and the duration of hospital stay in cardiothoracic and orthopedic surgery ^{75–77}. Studies on preoperative eradication therapy of *S. aureus* in vascular surgery are lacking. In **Chapter 2**, the effect of screening and eradication of *S. aureus* on the development of surgical site infections is assessed. A prospective cohort of vascular surgery patients was compared to a control group on the incidence of postoperative SSI.

Building on the previous chapter, **Chapter 3** examines the effect of *S. aureus* eradication treatment in aortoiliac surgery in an expanded cohort of vascular surgery patients.

Risk factors for surgical site infections in vascular surgery

Hybrid revascularization combines open lower extremity surgery and endovascular procedures to simultaneously treat atherosclerotic lesions on multiple levels in patients with PAD. Performing common femoral endarterectomy and iliac or (infra-)popliteal angioplasty procedures in a single setting, the need for separate interventions and/or major surgery may be eliminated. This hybrid therapy appears to be a safe, less invasive strategy for multi-level stenosis revascularization, despite longer duration of surgery ^{78–80}. **Chapter 4** compares the development of SSI after common femoral artery endarterectomy (CFE) and hybrid revascularization procedures.

Though different in nature, aneurysmal and occlusive disease are both subject to open vascular surgery and, with that, prone to SSIs ^{45,81–86}. Since occlusive arterial disease is related to microcirculatory dysfunction, it might have a negative impact on wound healing, and therefore the development of SSI ^{87–89}. No known comparison of infection risk between aneurysmal or occlusive vascular disease is found in the literature. **Chapter 5** evaluates the incidence and nature of SSI following open aortoiliac surgery for either aneurysmal or occlusive arterial disease.

SSI occurs both after open and endovascular aneurysm surgery, though details regarding outcomes after SSI in these groups are unknown in the literature^{81–83}. A severe complication after abdominal aneurysm surgery is aortic graft infection, which can lead to re-intervention, amputation and death. A relation between perioperative infections and aortic graft infections has been suggested, but evidence has been inconclusive. In **Chapter 6**, the incidence, outcome and link between SSI and graft infection in open and endovascular abdominal aortic aneurysm surgery are evaluated.

Chapter 7 provides a summary and general discussion of this thesis, as well as future perspectives. **Chapter 8** provides an impact paragraph, describing this work's scientific value and its impact on medical practice.

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Chapter 2

Evaluation of *Staphylococcus aureus* Eradication Therapy in Vascular Surgery

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ABSTRACT

Introduction

Surgical site infections (SSI) are a serious complication in vascular surgery which may lead to severe morbidity and mortality. *Staphylococcus aureus* nasal carriage is associated with increased risk for development of SSIs in central vascular surgery. The risk for SSI can be reduced by perioperative eradication of *S. aureus* carriage in cardiothoracic and orthopedic surgery. This study analyzes the relation between *S. aureus* eradication therapy and SSI in a vascular surgery population.

Methods

A prospective cohort study was performed, including all patients undergoing vascular surgery between February 2013 and April 2015. Patients were screened for *S. aureus* nasal carriage and, when tested positive, were subsequently treated with eradication therapy. The presence of SSI was recorded based on criteria of the CDC. The control group consisted of a cohort of vascular surgery patients in 2010, who were screened, but received no treatment.

Results

A total of 444 patients were screened. 104 nasal swabs were positive for *S. aureus*, these patients were included in the intervention group. 204 patients were screened in the 2010 cohort. 51 tested positive and were included in the control group. The incidence of *S. aureus* infection was 5 out of 51 (9.8%) in the control group versus 3 out of 104 in the eradication group (2.2%; 95% confidence interval 0.02-1.39; $P=0.13$). A subgroup analysis showed that the incidence of *S. aureus* infection was 3 out of 23 (13.0%) in the control group in central reconstructive surgery versus 0 out of 44 in the intervention group ($P=0.074$). The reduction of infection pressure by *S. aureus* was stronger than the reduction of infection pressure by other pathogens (exact maximum likelihood estimation; OR = 0.0724; 95 % CI: 0.001-0.98; $p = 0.0475$).

Conclusion

S. aureus eradication therapy reduces the infection pressure of *S. aureus*, resulting in a reduction of SSIs caused by *S. aureus*.

INTRODUCTION

Staphylococcus aureus nasal carriage is associated with an increased risk for developing a health care-related infection with this micro-organism. This effect has been described in several populations, e.g. cardiac surgery, orthopedic surgery and peritoneal dialysis ¹⁻³. Preoperative screening and subsequent treatment of nasal *S. aureus* carriers with mupirocin and chlorhexidine reduces the risk of developing hospital-acquired infections as well as the duration of hospital stay ^{4,5}. A cost benefit analysis shows that this strategy is highly cost-effective ⁶.

In vascular surgery the relation between nasal carriage of *S. aureus* and the development of surgical site infections (SSI) has been found for patients undergoing central vascular reconstruction surgery. In other peripheral vascular procedures this relation has not been demonstrated ⁷. Little is known about the result of treatment of carriage in the field of vascular surgery, even though it has been shown that surgical site infections are related to serious morbidity and mortality ^{8,9}. This study evaluates the effect of nasal screening and subsequent eradication therapy in vascular surgical procedures. The aim of this study is to investigate whether nasal screening and eradication of *S. aureus* reduces the incidence of surgical site infections caused by this micro-organism.

PATIENTS AND METHODS

A clinical audit was performed on all patients undergoing vascular surgery between February 2013 and April 2015 in the Amphia Hospital, Breda, The Netherlands, as part of a quality assurance study.

The surgical procedures included central reconstructions for abdominal aortic aneurysms and occlusive disease (endovascular [EVAR] and open), peripheral bypass procedures (autologous and polytetrafluoroethylene [PTFE]), endarterectomies of the femoral and carotid artery, embolectomies and artero-venous access procedures. All patients received 2 grams of cefazolin as standard preoperative antibiotics.

Baseline characteristics including gender, age and risk factors such as diabetes mellitus, smoking, hypertension, end stage renal failure and congestive heart failure were obtained from all included patients. Type of surgery (central or peripheral) and the use of an implant were also assessed.

As described in detail previously ⁷, all patients were screened for *S. aureus* on the day that they were admitted to the vascular surgery department of our hospital. Screening was performed by using a dry, sterile swab, which was rotated four times in each nostril. The

swab was placed in saline and subsequently centrifuged. Part of the sample was processed for polymerase chain reaction (PCR) on the presence of *S. aureus*, and part was inoculated onto a blood agar plate, to allow nasal and infecting strains to be compared in case a surgical site infection did occur.

The GeneXpert MRSA/SA Assay (Cepheid, Sunnyvale, CA) is a real-time PCR-based method, capable of both identifying *S. aureus* and differentiating whether a *S. aureus* is methicillin-susceptible (MSSA) or methicillin-resistant (MRSA) ¹⁰⁻¹³.

Patients who were tested positive for *S. aureus* were subsequently treated with eradication therapy.

Eradication therapy consisted of mupirocin ointment 2% (Bactroban, GlaxoSmithKline) in combination with chlorhexidine gluconate soap, 40mg per milliliter (Hibiscrub, Mölnycke). Bactroban ointment was applied twice a day, and Hibiscrub was used daily for a total body wash. The duration of the treatment was 5 days.

Patients were followed prospectively for the development of SSIs for at least 30 days. SSI was defined in agreement with the Centers for Disease Control's criteria ¹⁴.

The main criteria are the presence of pain, heat, swelling and/or redness around the wound within 30 days after the initial procedure, as well as the presence of a positive culture, drainage of the wound or the presence of pus upon performing a diagnostic puncture. All infections were confirmed by a physician.

The control group consisted of a cohort of patients who underwent vascular surgery at the Amphia Hospital between January 1st and December 31st 2010 and were screened for *S. aureus* nasal carriage and prospectively followed for the development of surgical site infections as described above, but who did not receive any eradication treatment.

Screening was performed as part of the infection control strategy of the Amphia hospital using non-invasive sampling and anonymized data analysis. Approval of the medical ethical committee and informed consent were not applicable in this evaluation of clinical practice.

Statistical analysis was performed using SPSS software v21.0 (SPSS Inc., Chicago, IL, USA) and LogXact (Cytel, Cambridge, MA, USA). A binary logistic regression with a fisher's exact test was used to determine significance. A P-value of < 0.05 was considered significant.

RESULTS

Patient population

Between February 1st 2013 and April 31th 2015, 592 patients were admitted to the hospital who underwent vascular surgery. Of these patients, 148 patients were not screened due to emergency admissions or non-compliance of staff and patients. Of the 444 patients who were screened, 104 (23.4%) grew *S. aureus* and were subsequently treated. These patients are further indicated as the intervention group.

In the 2010 cohort, 326 patients were admitted to the hospital, of which 122 were not screened, 153 screened negative and 51 (25.0%) screened positive but were not treated. These 51 patients were considered as a historical control group.

Patient characteristics

The percentage of ASA 2 patients was significantly lower in the intervention group. No differences were observed in the rest of baseline characteristics between the intervention and historical control group (Table 1).

Table 1. Baseline characteristics of the 155 study patient characteristics

Characteristics	Screened positive, not treated (n= 51)	Screened positive, treated (n=104)	P-value (Chi-square test)
Mean (SD) age	71.5 (10.6)	69.5 (8.6)	0.216
Sex, Male/Female (% male)	39/12 (77)	78/26 (73)	1.000
Peripheral procedure N/ (%)	28 (55)	60 (58)	0.863
Implant used N/ (%)	35 (69)	70 (67)	1.000
Risk factor N/ (%)			
Mean (SD) Body Mass Index	24.8 (6.3)	26.0 (5.0)	0.222
Mean (SD) Length of surgery in minutes	171 (72)	151 (61)	0.084
ASA (%)			0.023
2	12 (24)	47 (46)	
3	36 (72)	51 (50)	
4	2 (4)	2 (4)	
Smoking	19 (37)	36 (34)	0.858
Diabetes mellitus	20 (39)	37 (35)	0.724
Hypertension	27 (53)	54 (52)	1.000
End Stage Renal failure	4 (8)	7 (7)	0.752
Congestive heart failure	24 (47)	46 (44)	0.864

Infection rates

There were 6 (11.7%) surgical site infections in the non-treated group (n=51) versus 13 (13.6%) in the treated group (n=104) (OR 1.09, 95%CI 0.62-2.029 P= 0.97). In 8 of these surgical site infections, wound swabs tested positive for *S. aureus*. 5 (9.8%) occurred in the non-treated group versus 3 (2.2%) in the treated group (OR 0.37; 95%CI 0.02-1.39; P=0.13) (Table 2). There were no cases of Methicillin resistant *S. aureus* (MRSA). The reduction of infection pressure by *S. aureus* is greater than the reduction of infection pressure by other pathogens (exact maximum likelihood estimation; OR = 0.0724; 95 % CI: 0.001-0.98; p = 0.0475).

Table 2. Infection rates in intervention and control group

	Positive, not treated (n=51)	Positive, treated (n=104)	Odds Ratio	95% CI; P value (chi-square test)
Total SSI (%)	6 (11.8)	13 (12.5)	1.09	0.62-2.029; P= 0.97
Non <i>S. aureus</i> SSI (%)	1	10		
Type				
<i>Pseudomonas aeruginosa</i>	1			
<i>Staphylococcus capitis</i>		1		
<i>Escherichia coli</i>		1		
<i>Proteus mirabilis</i>		1		
<i>Morganella morganii</i>		1		
<i>Enterobacter cloacae</i>		1		
<i>Streptococcus anginosus</i>		1		
Unable to obtain culture (superficial infection)		4		
<i>S. aureus</i> SSI (%)	5 (9.8)	3 (2.8)	0.37	0.02-1.39; P= 0.13

Stratified analysis of infection rate

In central reconstructive surgery (n=67), no cases of *S. aureus* SSI appeared in the intervention group, opposed to 3 (13.0%) in the historical control group (p= 0.04, The exact one-sided p-value is used here, since the proper 95%-confidence interval corresponds with a one-sided 97.5%-confidence interval, because there is no lower limit [a value of 0 SSIs was found in the intervention group]. In this case, significance should be tested against an alpha value of 0.025. Therefore, significance is not reached in this case.) In peripheral procedures, 3 (5.0%) *S. aureus* SSIs were encountered in the intervention group, compared to 2 (7.1%) *S. aureus* infections in the control group (P=0.651) (Table 3).

Table 3: Stratified infection rates

Surgery type		<i>S. aureus</i> infection rate	P-value (chi-square test)
Central reconstruction (n= 67)	Treated (n=44)	0 (0.0%)	0.04
	Non treated (n=23)	3 (13.0%)	
Peripheral procedure (n=88)	Treated (n=60)	3 (5.0%)	0.651
	Non treated (n=28)	2 (7.1%)	
Implant (n=105)	Treated (n= 70)	1 (1.4%)	0.041
	Non treated (n= 35)	4 (11.4%)	
No implant (n=50)	Treated (n= 16)	1 (6.3%)	1.000
	Non treated (n= 34)	2 (5.9%)	

DISCUSSION

This clinical evaluation shows that surgical site infections are a relatively frequent complication in vascular surgery and that a large percentage (42%) is caused by *S. aureus*. Overall, there is no significant relation between eradication of *S. aureus* and the occurrence of surgical site infections. Analysis shows that the infection pressure by *S. aureus* is greatly reduced by eradication treatment in comparison to the overall infection pressure, while the general infection pressure does not seem to diminish. This results in a reduced incidence of *S. aureus* infections, while not lowering the overall SSI rate. This could be explained due to the competing nature of infection pathogens. When the growth and virulence of *S. aureus* are removed from the surgical site's bacterial 'pool', other pathogens which do not react on our proposed eradication therapy are given the chance to flourish and cause a surgical site infection.

The infection pressure of *S. aureus* in vascular surgery can be significantly lowered by using mupirocin and chlorhexidine gluconate soap eradication therapy in *S. aureus* carriers. Recent research shows that a reduction in the amount of *S. aureus* SSIs reduces 1-year mortality in surgical patients undergoing clean procedures ¹⁵. Eradication treatment not only reduces mortality, it also substantially reduces hospital costs in patients undergoing clean surgery ¹⁶. This shows that a cheap and minimally invasive treatment can greatly reduce patient mortality, as well as substantially lower hospital costs. Other authors have opted for a treat-all strategy instead of the screen-and-treat strategy that was used in this study. While treating all patients and omitting the screening process is a lot cheaper than the screen-and-treat method, the treat-all strategy is associated with a high rate of unnecessary and therefore unethical treatments which increase the probability of the development of bacterial resistance ^{6,17}.

When applying eradication therapy to *S. aureus* nasal carriers who undergo central reconstructive surgery, it might have a greater reduction in SSI rate than patients using eradication therapy before undergoing a peripheral vascular procedure. A possible reason for the difference in effect of treatment between the central reconstructive surgery group and the peripheral surgery group is the higher prevalence of leg ulcers in the peripheral surgery group before and during the surgical procedure. The main reason to perform peripheral vascular surgery is the presence of critical limb ischemia (CLI). In recent literature, the prevalence of patients with CLI and leg ulcers (Fontaine classification stage IV) was estimated as 0.18% ¹⁸. These ulcers may often be polymicrobially infected with gram positive cocci, gram negative rods and anaerobic organisms, which may easily spread to the surgical incision site in the groin area of the affected leg ¹⁹. It is plausible that the introduction of these bacteria to the surgical wound will negate any positive effect the patient could have obtained from eradication therapy for *S. aureus*. In the central reconstruction group, the prevalence of leg

ulcers, and therefore bacterial influx from the leg, is not higher than in the healthy population, since there is no obstruction of blood flow to the lower limb.

Another explanation for the lack of reduction of SSIs in treated *S. aureus*-carriers who undergo peripheral surgery is the recent implementation of a bundle of care in the Amphia Hospital. This bundle of care, which was implemented to reduce SSIs, lowered the incidence of SSIs in patients who underwent vascular surgery by 44% in two years' time (from 14.9% to 8.4%)²⁰. A further reduction of this already low prevalence of infections might be hard to achieve.

Though it was not the scope of this research, more information regarding *S. aureus* eradication therapy and its benefits in vascular surgery could be obtained by researching length of hospital stay, graft patency and the incidence of resurgery. Potential bias includes selection bias due to the fact that 148 patients were not screened. A number of these patients were not screened due to emergency admissions, which might lead to an over-estimation of the effect of eradication therapy in high-risk patients, since most of our hospital's acute vascular surgery is performed on patients with a high percentage of comorbidity or patients with a large medical history of vascular illness and/or vascular procedures.

Taking all this into consideration, mupirocin and chlorhexidine-based eradication therapy might provide a minimal invasive, cost-effective means to reduce complications arising from SSIs in vascular surgery.

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3

Chapter 3

Perioperative nasal eradication therapy prevents *Staphylococcus aureus* surgical site infections in aortoiliac surgery

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ABSTRACT

Introduction

Surgical site infections (SSI) cause considerable morbidity and mortality among patients undergoing vascular surgery. Preoperative screening and subsequent treatment of nasal *Staphylococcus aureus* carriers with mupirocin and chlorhexidine reduces the risk of developing SSIs in cardiothoracic and orthopedic surgery. The aim of this study was to investigate the effect of this screen and treat strategy on the development of SSI in patients undergoing aortoiliac surgery.

Methods

A prospective study was performed, including an intervention cohort comprised of all patients undergoing aortoiliac surgery from February 2013 to December 2016. Before surgery, patients were screened for *S. aureus* nasal carriage and, if tested positive, were subsequently treated with eradication therapy consisting of mupirocin nasal ointment and chlorhexidine body washes. The presence of SSI was recorded based on criteria of the Centre for Disease Control. A historic control group was used, consisting of aortoiliac surgery patients in 2010 who tested positive for *S. aureus*, but received no treatment.

Results

A total of 374 patients in the study cohort were screened of which 75 (20.1%) tested positive for *S. aureus*. Of these patients, 68 were treated with eradication therapy. In the 2010 cohort, 22 out of 140 (15.7%) patients were positive. The incidence of *S. aureus* infection was 0 out of 75 in the treatment group versus 3 out of 22 (13.6%) in the control group ($P = .010$). Both thirty-day mortality (1.3% vs. 13.6%, $P = .035$) and the rate of re-interventions (12.0% vs. 31.8%) were significantly lower in the treatment group.

Conclusion

We conclude that *S. aureus* nasal screening and eradication therapy with mupirocin and chlorhexidine is a preventive strategy to reduce *S. aureus* SSI and its complications in aortoiliac surgery.

INTRODUCTION

Surgical site infections (SSI) are a considerable cause of morbidity and mortality among patients undergoing vascular surgery. The overall incidence of SSI ranges from 1-2% after open or endovascular aortic interventions to 10-20% after lower limb bypass surgery ¹. Deep SSI is associated with aortic graft infection, which can lead to sepsis, secondary aortic rupture, and death. Surgical intervention is often required, with reported 30-day mortality as high as 28% ².

Staphylococcus aureus is the primary cause of deep SSI, and its infections can be particularly challenging to treat because of evolving resistance to antimicrobial drugs ^{3,4}.

S. aureus nasal carriage is a known risk factor for developing SSI in several populations, including patients undergoing cardiac surgery and orthopedic surgery ⁵⁻⁷. Preoperative screening and subsequent treatment of nasal *S. aureus* carriers with mupirocin and chlorhexidine reduces the risk of developing hospital-acquired infections as well as the duration of hospital stay in cardiothoracic and orthopedic surgery ^{8,9}. This method has proven to be highly cost-effective ¹⁰.

We demonstrated the relation between *S. aureus* nasal carriage and development of SSI in patients undergoing aortoiliac reconstructive procedures, but not in peripheral vascular surgery ¹¹. Recent research has shown that *S. aureus* eradication therapy may reduce *S. aureus*-related SSI in patients undergoing aortoiliac procedures, though the numbers treated were small ¹². At this moment, there is no conclusive evidence concerning the reduction of *S. aureus*-related SSIs using eradication therapy in aortoiliac surgery.

The aim of this study was to investigate the reduction of SSI in patients undergoing aortoiliac surgery after screening and eradication of *S. aureus*.

METHODS

A prospective surveillance was performed on all patients undergoing vascular surgery from February 2013 to December 2016 in the Amphia Hospital, Breda, The Netherlands, as part of the hospital patient-safety program.

Surgical procedures

The surgical procedures included central reconstructions for abdominal aortic or aortoiliac aneurysms and aortoiliac occlusive disease, both endovascular and open. Endovascular procedures included were endovascular aneurysm repair (EVAR) and embolectomy, while open procedures included aortic tube grafts, aortic bifurcation grafts (biiliac, bifemoral and

combined), unilateral aortoiliac and aortofemoral bypass grafts, aortoiliac interposition grafts and aortoiliac endarterectomies. Open access was gained either via laparotomy or lumbotomy. Endovascular procedures were performed by gaining open surgical access to the common femoral artery. Hybrid surgery cases using both open and endovascular techniques were not included. All patients received 2 grams of cefazolin as standard preoperative antibiotics.

Data gathering

Baseline characteristics were obtained from all patients. These included gender, age, American Society of Anesthesiologists (ASA) class, and patient-specific risk factors such as diabetes mellitus, smoking, hypertension, end-stage renal failure, congestive heart failure and body mass index. Recorded procedure-specific factors included type of surgery, location of incision, use of implants, proper administration of preoperative antibiotics, proper preoperative hair removal, perioperative normothermia, duration of surgery, blood loss during surgery and length of post-operative intensive care unit stay.

Screening and therapy

As described in detail previously ¹¹, all patients were screened for *S. aureus* in the outpatient clinic for elective surgery and on the day of admission to the vascular surgery department in case of acute surgery. Screening was performed by using a dry, sterile swab, which was rotated four times in each nostril. The swab was placed in saline and subsequently centrifuged. Part of the sample was processed for polymerase chain reaction (PCR) on the presence of *S. aureus*, and part was inoculated onto a blood agar plate, to allow nasal and infecting strains to be compared in case a surgical site infection did occur.

The GeneXpert MRSA/SA Assay (Cepheid, Sunnyvale, CA) is a real-time PCR-based method, capable of both identifying *S. aureus* and differentiating whether a *S. aureus* is methicillin-susceptible (MSSA) or methicillin-resistant (MRSA) ¹³⁻¹⁶.

Patients positive for *S. aureus* were subsequently treated with eradication therapy, consisting of mupirocin nasal ointment 2% (Bactroban, GlaxoSmithKline) in combination with chlorhexidine gluconate soap, 40mg per milliliter (Hibiscrub, Mölnlycke). Bactroban was applied in each nostril twice a day, and Hibiscrub was used daily for a total body wash. Treatment started on the day of hospital admission, 1 day before surgery, and continued for a total of 5 day ⁹.

Patients were followed prospectively for the development of SSIs for 90 days. Dedicated and specifically trained infection control personnel performed scoring of SSI. The presence of an SSI was ascertained by a microbiologist and a vascular surgeon ¹⁷. The main criteria for SSI, as defined by the criteria of the Centre for Disease Control ¹⁸, were the presence of heat,

swelling or pain around the wound within 30 days after the initial procedure and/or the presence of a positive culture, drainage of the wound or pus after a diagnostic puncture.

All aortoiliac surgery patients who underwent surgery from February 2013 to December 2016 were included in the treatment group. Patients in this group who tested positive for *S. aureus*, but did not undergo eradication treatment were included in the treatment group as part of an intention-to-treat analysis. The historical control group consisted of a cohort of patients who underwent aortoiliac surgery at the Amphia Hospital between January 1st and December 31st 2010 and were screened for *S. aureus* nasal carriage and prospectively followed for the development of surgical site infections as described above, but who did not receive any eradication treatment ¹¹.

Screening and treatment were performed as part of the infection control strategy of the Amphia hospital using non-invasive sampling and anonymized data analysis. The medical ethical committee decided this study did not fall under the scope of the Medical Research Involving Human Subjects Act.

Statistical analysis

Imbalances in baseline characteristics and procedure-related risk factors between the treated and control group were investigated using the t-test for continuous variables or Fisher's exact test for dichotomous variables. Efficacy analyses of the effect of treatment on *S. aureus* infection were performed using exact conditional logistic regression analysis, unadjusted as well as adjusted for confounding covariables. Effects were quantified by means of odds ratios (OR). Exact 1-sided p-values and confidence limits of the odds ratios were calculated. Point estimates were either conditional maximum likelihood estimates or median unbiased estimates if the odds ratio turned out to be on its boundary.

Statistical analysis was performed using SPSS software v21.0 (SPSS Inc., Chicago, IL, USA).). For the exact logistic regression analysis, we used LogXact (v 4.1, Cytel Software Corporation, 1989-2000). P-values used were two-sided, two-sided p-values of the exact tests were calculated as two times the exact one-sided p-values. A P-value below .05 indicated statistical significance.

As a study following up on our earlier research, part of these research methods match those of our earlier study ¹².

RESULTS

Population

From February 2013 to December 2016, 489 patients underwent aortoiliac surgery in our hospital. Of these patients, 374 were screened for *S. aureus* nasal carriage and 75 (20.1%) tested positive. A total of 68 patients received eradication therapy. All 75 patients were included in the treatment group. The reasons that seven patients were not treated while tested positive were: emergency admissions (n=3), staff non-compliance (n=2) or patient non-compliance (n=2).

In the 2010 cohort, 154 patients were admitted, of which 94 were screened and 22 (23.4%) tested positive but were not treated, according to the policy at that time. These *S. aureus*-positive, untreated patients were considered the control group.

Due to emergency surgery and non-compliance by staff or patients, there were patients left unscreened before surgery in both periods.

Patient characteristics

The two groups were comparable regarding most baseline characteristics (table 1). The treatment group contained a higher percentage of females and was characterized by a shorter mean duration of surgery. The treatment group includes five patients (6.7%) who underwent acute surgery. Two of these patients started the eradication therapy protocol on the day following surgery. Three were not treated, as mentioned above. Both groups showed equal distribution of incision locations.

Infection rates

As shown in table 2, there were 5 (6.7%) surgical site infections in the treatment group versus 3 (13.6%) in the control group ($P = .38$). In the treatment group there was one infection with *Pseudomonas aeruginosa*, two with *Enterobacter cloacae* and two wound cultures showed mixed flora. In the control group, all three infections were caused by *S. aureus*. There were no cases of *S. aureus* infection in the treatment group. The control group showed two *S. aureus* infections in an abdominal incision and one in a groin incision. The estimated crude effect of treatment on *S. aureus* infection was: OR = 0.07 (95 % CI: 0, 0.67; $P = .020$). There was no significant difference in non-*S. aureus* infection between the treatment (6.7%) and control group (0%, $P = .59$).

Secondary outcomes

The mean duration of hospital stay and the rate of re-admittance did not differ significantly. There was a lower rate of overall re-interventions in the treatment group (12.0%) compared to the control group (31.8%, $P = .046$). There was only one infection-related re-intervention, which occurred in the treatment group (1.3%). A deep SSI required the replacement of an infected aortic graft. Thirty-day mortality was significantly lower in the treatment group (1.3% vs 13.6%, $P = .035$), though these deaths were not infection-related. The cause of mortality was perioperative cardiac failure in 2 patients and uncontrollable perioperative bleeding in 1 patient in the control group. The one mortality in the treatment group was due to cerebrovascular infarction and irreversible mesenteric ischemia.

There was no difference in SSI incidence between patients with or without groin incisions (8.0% vs 8.3%, $P = 1.000$) or between patients undergoing open or endovascular surgery (12.0% vs 4.3%, $P = .27$).

DISCUSSION

This study aimed to assess the effect of screening for and eradication of *S. aureus* on the development of SSIs in aortoiliac surgery. No *S. aureus* infections were found after screening and eradication therapy. This result adds to the evidence provided by our previous research¹². The effect found in this population is comparable to that in previous studies in patients undergoing non-vascular surgery^{19,20}. The trends and effects seen in these studies combined with our report support the use of pre-operative mupirocin and chlorhexidine for the prevention of SSI in aortoiliac surgery. The World Health Organization's Global Guidelines for the Prevention of Surgical Site Infection gives a conditional recommendation suggesting treatment of surgery patients having *S. aureus* nasal carriage with peri-operative intranasal applications of mupirocin 2% with or without a chlorhexidine body wash²¹. Our results endorse this recommendation.

Table 1. Baseline characteristics of patients who tested positive for *S. aureus* nasal carriage

Characteristics	Control group (n= 22)	Treatment group (n=75)	P-value
Mean (SD) age	65.1 (11.2)	68.4 (9.1)	0.160 <i>b</i>
Sex, no. Male (% male)	20 (90.9)	56 (74.7)	0.144 <i>a</i>
Implant used N (%)	21 (95.5)	70 (93.3)	1.000 <i>a</i>
Mean (SD) Body Mass Index	25.7 (4.3)	25.3 (4.6)	0.723 <i>b</i>
ASA Score ≥ 3 (%)	16 (72.7)	42 (56.0)	0.275 <i>a</i>
Smoking (%)	11 (50.0)	24 (32.0)	0.276 <i>a</i>
Diabetes mellitus (%)	8 (36.4)	25 (33.3)	0.802 <i>a</i>
Hypertension (%)	16 (72.7)	41 (54.7)	0.148 <i>a</i>
End Stage Renal failure (%)	1 (4.5)	8 (10.7)	0.679 <i>a</i>
Congestive heart failure (%)	12 (54.5)	28 (37.3)	0.218 <i>a</i>
Procedure-related Risk factors			
Acute procedure (%)	0	5 (6.7)	0.585 <i>a</i>
Endovascular procedure (%)	10 (45.5)	37 (49.3)	0.811 <i>a</i>
- EVAR (% within group)	10 (100)	34 (91.9)	
- Embolectomy (% within group)		3 (8.1)	
Incision location			0.846 <i>a</i>
- Abdominal	6 (27.3)	19 (25.3)	
- Groin	10 (45.5)	37 (49.3)	
- Abdominal + groin	6 (27.3)	17 (22.7)	
- Abdominal + groin + peripheral	0	2 (2.7)	
Mean (SD) Length of surgery in minutes	177 (75)	145 (49)	0.011 <i>b</i>
Proper administration of preoperative antibiotics (%)	21 (95.5)	71 (94.7)	1.000 <i>a</i>
Proper preoperative hair removal (%)	17 (77.3) <i>c</i>	67 (89.3) <i>d</i>	0.127 <i>a</i>
Peroperative normothermia (%)	15 (68.2) <i>e</i>	57 (76.0) <i>f</i>	0.563 <i>a</i>

a Fisher's Exact Test*b* ANOVA*c* 5 cases missing*d* 6 cases missing*e* 4 cases missing*f* 13 cases missing

Table 2. Infection rates and secondary outcomes

	Control group (n= 22)	Treatment group (n=75)	P-value
Infection rate (%)	3 (13.6)	5 (6.7)	0.376
Deep infection (%)	0	2 (2.7)	0.596
<i>S. aureus</i> infection rate (%)	3 (13.6)	0	0.010
Duration of hospital stay (mean, SD)*	11.82 (10.37)	11.72 (12.26)	0.973
Re-intervention (%)	7 (31.8)	9 (12.0)	0.046
Re-admittance (%)	8 (36.4)	25 (33.3)	0.802
30-day mortality (%)	3 (13.6)	1 (1.3)	0.035

*including duration of readmissions

Although our cohort receiving eradication therapy developed fewer *S. aureus* SSIs, the overall infection rates were not significantly different. This phenomenon was observed in previous studies on eradication therapy, which saw a decrease in *S. aureus* SSI without a reduction in overall SSI ^{22–24}. Despite this, a reduction in *S. aureus* SSI reduces the one-year mortality rate in patients undergoing clean surgical procedures ²⁵. Besides a reduction in the mortality rate, eradication treatment substantially reduces hospital costs in this group ²⁶. This implies that screening and eradication of *S. aureus* is a minimally invasive way to reduce patient morbidity, deaths, and hospital costs. It could be argued that a treat-all strategy is more cost-effective and less invasive than a screen-and-treat strategy. However, with the ever-growing global problem of anti-microbial resistance, we believe it is unethical and potentially harmful to provide a large number of patients with a treatment that has no beneficial effect, as this increases the probability of the development of bacterial anti-microbial resistance ^{10,27}. The drawback of a screen and-treat strategy is that patients having emergency procedures are not included, because of the lack of time to perform the screening. This group probably should be treated without testing.

The eradication of *S. aureus* in the nares and washing the entire body in chlorhexidine results in a reduction of emerging SSI, contributing to the concept that *S. aureus* migrates from the nares to other areas of the skin, more specifically to the surgical site, where it can cause infection.

This research has evaluated the effect of eradication therapy in a subgroup of vascular surgery patients, and earlier research showed that eradication therapy does not reduce the risk of SSI in peripheral vascular surgery. Although the number of patients undergoing central reconstructions may be small, the significance of SSI reduction could be substantial. An infection in the abdominal region, superficial or deep, often marks the start of a long and complicated healing process. Superficial infections can induce dehiscence, abdominal fistulae, and even evisceration. Deep abdominal infections often lead to aortic graft infection, which frequently requires weeks or months of antibiotic therapy and may be a cause of the need for surgical graft replacement.

The potential biases of this study include selection bias caused by the 115 (23.5% of 489) patients who were not screened. Some of these patients were left unscreened because of the need for emergency admissions or for acute surgery, which might mean that our findings do not fully represent the high-risk acute vascular patient. It might be wise to treat these acute patients without screening, as this might reduce the risk of *S. aureus* SSI in a high-risk group, but this idea remains to be confirmed in future studies. Another cause of selection bias is the seven patients allocated to the treatment group who tested positive between 2013 and 2017 but were not treated. Three of these patients were not treated because of emergency admissions with immediate surgery; the other four had no apparent reasons treatment was avoided. We allocated these patients to the treatment group for an intention-to-treat analysis. After having observed that no *S. aureus* infections occurred in these seven patients, one could argue that an as-treated analysis would give a more conservative estimate of the treatment effect. When the seven *S. aureus*-positive, untreated patients are allocated to the control group, the estimated crude effect of treatment on *S. aureus* infection is OR 0.104 (95% CI 0–0.996; $p = 0.0496$). So, in the more conservative as-treated analysis, the conclusion of a significant effect of eradication therapy still stands.

One concern with the different time periods for the cohorts is that other factors, such as more SSI awareness and new hygiene measures, might have led to a general reduction in SSIs between 2010 and 2017. We analyzed the data of all aortoiliac surgery patients treated in this time period, regardless of *S. aureus* screening, and observed no difference in SSI incidence between patients treated in 2010 (nine of 141; 6.4%) or after 2013 (26 of 488; 5.3%; $p = 0.68$).

In our study, most patients were admitted the day before surgery and started eradication therapy on that day. Although outpatient eradication treatment is an option, lack of patient

compliance could be a problem. We found only one article that reported compliance in outpatient eradication treatment. The Mupirocin Study Group had patients keep diaries to register each mupirocin application, with a reported noncompliance rate of 2.7%²⁴. Wertheim et al. reported a 0.68% lack of compliance rate²⁸. Given the high reported outpatient compliance rate, we believe the indication of earlier hospital admission for eradication therapy must be weighed against the added cost of earlier admittance.

Finally, there is the estimated OR ratio, with the lower confidence limit on its boundary being zero. Also, the limitation of a historical control group has to be mentioned. We tried to adjust for possibly confounding variables using exact conditional logistic regression analysis. Two variables were selected for the model along with treatment of the total set presented in Table 1 based on a univariable p value <0.50: Age (p = 0.061) and smoking (p = 0.22), with, respectively, a negative and positive effect on *S. aureus* infection.

The effect of these variables appeared to dominate the treatment effect (p = 0.29) in the model in explaining the infection risk. With only three events, the conclusions of this analysis might be inherently flawed, so further results will not be presented. The result that especially young smokers experienced a high infection risk has to be considered hypothesis generating. Larger observational studies with more infections will yield a better adjustment and larger precision of the point estimates of the treatment effect. The reason we did not expand our current cohort to such numbers is the relative rarity of aortoiliac surgery patients who test positive for *S. aureus*. With an inclusion rate of 1.5 patients per month, we felt it would be unwarranted to prolong the publishing of the results by years for a small benefit in confidence intervals. With the results of this study, supported by evidence in other surgical fields^{19,20}, it can be doubted whether a large, randomized trial on this subject would be ethical.

We conclude that *S. aureus* nasal screening and eradication therapy with mupirocin and chlorhexidine will reduce *S. aureus* SSI and its complications in aortoiliac surgery.

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4

Chapter 4

Infection risk following common femoral artery endarterectomy versus a hybrid procedure

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ABSTRACT

Introduction

Hybrid revascularization combines open lower extremity surgery and endovascular procedures to simultaneously treat atherosclerotic lesions on multiple levels in patients with peripheral arterial occlusive disease. Hybrid surgery appears to be a safe strategy for multilevel stenosis revascularization, though the risk of surgical site infection (SSI) has not been clearly investigated. This study evaluates the development of SSI following common femoral artery endarterectomy (CFE) and hybrid revascularization procedures.

Methods

A retrospective study was performed including all patients undergoing common femoral artery endarterectomy (CFE), as standalone or as part of a hybrid procedure, due to peripheral arterial occlusive disease between January 2013 and December 2016. Preoperative, intraoperative, clinical and follow-up information was gathered prospectively and reviewed retrospectively. The presence of SSI was recorded based on criteria of the CDC.

Results

A total of 229 CFEs were performed. 132 as a standalone procedure, 65 combined with iliofemoral angioplasty and 32 combined with peripheral angioplasty. 19 patients (8.3%) developed a SSI, of which four were deep infections. Ten infections (7.6%) occurred in the CFE-only group, five (7.7%) in the iliofemoral hybrid group and four (12.5%) in the peripheral hybrid group ($p=0.65$). Five patients (2.1%) required surgery to control the infection. The mean duration of stay was 5 days for patients without SSI versus 20 days for patients who developed a SSI ($p<0.0001$).

Conclusion

The hybrid procedure combining open femoral endarterectomy with endovascular revascularization is a safe procedure with no significant differences in infection rates between open surgery, central or peripheral hybrid revascularization.

INTRODUCTION

Ever since the introduction of percutaneous transluminal angioplasty (PTA) the indications for endovascular treatment of peripheral arterial occlusive disease (PAD) have greatly increased ^{1,2}. Also, considerable progress has been made in the expertise with which it is applied. Recent literature shows that an endovascular approach for symptomatic PAD is associated with improved amputation-free and overall survival both short and long term with a slightly increased risk of subsequent intervention ³.

PAD is often associated with a multilevel presence of occlusive lesions. The combination of iliac or popliteal occlusions and femoral artery bifurcation disease are therefore frequently seen ⁴. Femoral bifurcation lesions are not generally suitable for endovascular treatment, due to the difficulty of gaining ipsilateral vascular access and the bulky nature of the lesions. Surgery, by way of femoral endarterectomy (CFE) is still considered the gold standard treatment for common femoral artery occlusions ¹.

Hybrid revascularization combines open lower extremity surgery and endovascular procedures to simultaneously treat atherosclerotic lesions on multiple levels. By combining common femoral endarterectomy and iliac or (infra-)popliteal PTA procedures in a single setting, the need for separate interventions and/or major surgery may be eliminated. This hybrid therapy appears to be a safe, less invasive strategy for multi-level stenosis revascularization ⁵⁻⁷.

Postoperative surgical site infection (SSI) of the groin incision used in CFE and hybrid procedures may lead to longer hospital stay, increased mortality and increased morbidity, such as graft loss or (major) amputation. Besides the enormous healthcare costs related to SSIs, the quality of life (QoL) may suffer dramatically ⁸.

The objective of this study was to evaluate the development and impact of complications following CFE and hybrid procedures in our hospital and to define predictive factors for the occurrence of surgical site infection.

METHODS

Design

A retrospective study was performed including all patients undergoing femoral endarterectomy due to peripheral arterial occlusive disease between January 2013 and December 2016 in the Amphia Hospital, Breda, The Netherlands.

Patients and data collection

Patient data was gathered based on operation-specific codes, including those patients who only underwent a CFE during that procedure. Patients who underwent a CFE combined with bypass surgery as part of aortic repair surgery were excluded. All patients who were scored as undergoing a hybrid procedure were treated with a femoral endarterectomy and subsequent PTA in one setting.

Preoperative, intraoperative, clinical and follow-up information was gathered prospectively and reviewed retrospectively by reviewing medical files in the electronic medical record.

All patients were evaluated preoperatively with a complete medical history, physical examination, ankle brachial index (ABI) and magnetic resonance angiogram (MRA) with three-dimensional reconstruction imaging (patients not eligible for MRA were assessed with computed tomographic angiography). Fontaine classification was used to determine the disease category upon presentation.

Patients were included based on individual limbs; patients undergoing procedures on different legs were included twice. Patient specific characteristics that were gathered include gender, age, classification of PAOD (Fontaine), American Society of Anesthesiologists Physical Status classification (ASA-score), and risk factors such as smoking, diabetes mellitus, hypertension, renal failure and congestive heart failure. All factors were collected as they were on the day of surgery.

Data was gathered by the treating physician regarding surgery duration, length of hospital stay, the use of a vascular patch, occurrence of post-operative infection, reintervention within 3 months, readmission and mortality.

Scoring a surgical site infection was performed by dedicated and specifically trained infection control personnel. The presence of a SSI was ascertained by a microbiologist and a vascular surgeon ⁸. The main criteria for SSI, as defined by the criteria of the Centre for Disease Control ⁹, were the presence of heat, swelling or pain around the wound within 30 days after the initial procedure and/or the presence of a positive culture, drainage of the wound or pus after a diagnostic puncture. Superficial SSI was defined as an infection confined to the skin and subcutaneous tissue, while deep SSI were scored when the infection affected the perimuscular tissue or deeper organs.

Statistical analysis was performed using SPSS software version 19.0.0 (SPSS Inc., Chicago, IL, USA). Pearson Chi-square test was performed to test significance. A P-value of <0.05 was considered significant.

Surgical procedures

All procedures were performed at the Amphia Hospital, Breda, The Netherlands. The team of vascular surgeons both screened and selected patients and carried out the procedures. All femoral endarterectomies were performed in a regular operating room. Hybrid procedures were performed using a mobile C-arm for imaging support. All procedures were performed under general anesthesia. All patients received 2 grams of cefazolin as standard preoperative antibiotic prophylaxis.

The choice of using a patch in closing the femoral arteriotomy was based on the peroperative assessment of the surgeon. All patches were of bovine material (Vascu-Guard®, Synovis®).

All endovascular procedures were performed using a Terumo® sheath. A Cordis® Powerflex Pro PTA catheter (Johnson&Johnson) was used for angioplasty. In case of stenting, a balloon-expandable stent (Genesis®, Palmaz®) was used most often. In some cases, self-expanding stents were used (S.M.A.R.T. Control®, Cordis®).

All patients were treated with heparin during the procedure. The days following the procedure, patients were treated with prophylactic doses of low molecular weight heparin (Fraxiparine®).

Follow-up

All patients were followed for a period of 3 months. Follow-up consisted of clinical examination by a vascular surgeon. Additional imaging was only performed upon suspicion of complications. Patients were informed to immediately contact a doctor when signs of infection were present.

Statistical analysis

A Pearson χ^2 test was used to compare categorical variables; continuous variables were analyzed using independent t-tests. Logistic regression was used to evaluate risk factors. Statistical analysis was performed using SPSS software v24.0 (SPSS Inc., Chicago, IL, USA). P-values used were 2-sided, unless explicitly mentioned as 1-sided. A P-value below 0.05 (or a 1-sided P-value below 0.025) indicated statistical significance.

RESULTS

Patient population

Between January 1st 2013 and December 31st 2016, 229 patients underwent femoral endarterectomy, with or without simultaneous endovascular angioplasty as the only

procedure (without concomitant bypass or aortic repair surgery). Four of these patients underwent a CFE on both legs within this timeframe. These patients were included twice, once for each procedure. Figure 1 shows a flowchart depicting the numbers of patients excluded and the reasons for exclusion. Most procedures were performed in patients with gradual development of PAD (88%), with 28 patients (12%) being operated following an acute occlusion.

Patient characteristics

Patient-specific characteristics are described in table 1. The group undergoing iliofemoral angioplasty had a higher proportion of active smokers. Patients who underwent a peripheral angioplasty were more likely to have diabetes and critical limb ischemia. Duration of surgery was longer for hybrid procedures compared to only femoral endarterectomy. Vascular patches were used in 84% of all patients. There was no difference in patch use between the groups.

Table 1. Patient characteristics

Patient Characteristics (n=228)	Femoral endarterectomy (n=132)	Hybrid, central (n=65)	Hybrid, peripheral (n=32)	P-value
Age in years, mean (SD)	69.3 (9.0)	69.5 (9.8)	72.0 (9.4)	0.32
Sex, no. male (%male)	77 (58)	45 (69)	21 (66)	0.30
Critical limb ischemia (% within group)	47 (36)	25 (39)	18 (56)	0.10
ASA ≥ 3 (%)	90 (70)	44 (68)	21 (68)	0.92
Smoking (%)	41 (31)	28 (43)	10 (31)	0.23
Diabetes mellitus (%)	40 (30)	16 (24)	13 (41)	0.27
Hypertension (%)	105 (80)	45 (69)	22 (69)	0.19
Chronic renal disease (GFR <30) (%)	7 (5)	1 (2)	1 (3)	0.42
Congestive heart failure (%)	68 (51)	26 (40)	17 (53)	0.27
Duration of surgery in minutes, mean (SD)	111 (44)	156 (47)	156 (35)	<0.001
Use of vascular patch (%)	106 (80)	57 (88)	29 (91)	0.221

Postoperative outcome

Overall, nineteen patients (8.3%) developed a SSI. As presented in table 2, ten (7.6%) after CFE-only surgery, five (7.7%) after central hybrid surgery and four (12.5%) after peripheral hybrid surgery ($p=0.65$). Four deep SSIs occurred, of which two were in the CFE-only group (1.5%) and two occurred after peripheral hybrid surgery (6.3%, $p=0.08$). Five patients required surgical exploration of the groin area to control the infection, two in both the

peripheral group (6.3%) and CFE-only group (1.5%) and one in the iliofemoral group (1.5%, $p=0.24$). Four re-interventions consisted of deep exploration of the groin area, in which pus was found surrounding the femoral artery. One of these patients required three additional operations for infection control, including muscular transposition and skin transplants. One patient underwent resection of infected fatty necrosis in the incision area. Fourteen SSIs did not require a re-intervention. Seven were treated as outpatients with amoxicillin and clavulanic acid, four were re-admitted for antibiotic treatment and three were treated by abscess drainage in the emergency room. A culture was obtained from 13 patients. The isolated pathogens were *Streptococcus dysgalactiae* (6), *Proteus mirabilis* (3) *Escherichia coli* (2), *Pseudomonas aeruginosa* (1) and mixed flora (1). The mean time from surgery to SSI was 17.7 days (range 7-36). There were more infection related readmissions in the peripheral hybrid group (9.4%) compared to central hybrid (3.1%) or CFE-only (2.3%), though this difference is not statistically significant ($p=0.14$).

The mean duration of stay was 6.5 days (range 1-119 days). Patients who developed a SSI had a mean duration of stay of 20 days (13 days when one outlier of 119 days was removed from the analysis), compared to 5.1 days for patients who did not develop a SSI ($p<0.001$ in both instances). Length of stay did not differ significantly between performed procedures.

A logistic regression analysis showed no statistically significant determinants for developing SSI, though a trend was seen towards the influence of diabetes mellitus on the development of SSI (Odds ratio 2.68, 95% confidence interval 0.98 – 7.33, $p=0.055$). The full results are portrayed in table 3.

Mortality within thirty days occurred in five patients (2.1%), three in the CFE-only group and one in each hybrid group. One of these patients underwent a femoral endarterectomy six hours after a bilateral aorto-iliac embolectomy and PTA combined with femoropopliteal bypass. A re-occlusion of both legs occurred, without further therapeutic options, after which the patient rapidly passed away. One patient suffered a massive cerebral infarction short after discharge, and one died of multi-organ failure following a combined uro- and pneumosepsis. One patient developed a re-occlusion of the common iliac artery after which amputation was deemed the only viable therapy. This patient refused limb amputation and opted for euthanasia instead.

Table 2. Postoperative outcome between surgical procedure groups

	Femoral endarterectomy (n=132)	CFE+ Central PTA (n=65)	CFE+ Peripheral PTA (n=32)	P-value
Surgical site infection (%)	10 (7.6)	5 (7.7)	4 (12.5)	0.65
- Superficial infection (%)	8 (6.1)	5 (7.7)	2 (6.3)	0.08
- Deep infection (%)	2 (1.5)	0	2 (6.3)	
Infection related reintervention (%)	2 (1.5)	1 (1.5)	2 (6.3)	0.24
Infection related readmission (%)	3 (2.3)	2 (3.1)	3 (9.4)	0.14
Length of hospital stay (days), mean (SD*)	6.6 (11.5)	5.9 (6.5)	7.8 (7.6)	0.67
Mortality <30d (%)	3 (2.3)	1 (1.5)	1 (3.1)	0.88

*Standard deviation

Table 3. Outcomes of logistic regression of determinants for surgical site infection

Covariate	Adjusted odds ratio	95% Confidence Interval	P-value
Male sex	1.31	0.48 – 3.58	0.60
Smoking	0.60	0.18 – 1.98	0.40
Diabetes mellitus	2.68	0.98 – 7.33	0.06
Hypertension	1.66	0.43 – 6.51	0.67
Critical limb ischemia	1.93	0.71 – 5.23	0.20
Use of vascular patch	1.81	0.36 – 9.18	0.47
Duration of surgery	1.00	1.00 – 1.00	0.15
Hybrid surgery	2.13	0.62 – 7.25	0.23

DISCUSSION

Our study shows that the hybrid femoral endarterectomy, like the standalone common femoral artery endarterectomy, is a safe procedure with low perioperative mortality with comparable SSI incidence. The observed 30-day mortality in our study matches the lower range of that described in contemporary literature^{10–12}. While recent studies show good 2-year patency rates of hybrid femoral endarterectomy (59–75%), only one study reported differences in SSI rates between open and hybrid surgery^{13,14}. Dosluoglu et al. reported 15.4% infection after open endarterectomy and 7.5% after hybrid surgery. Chang et al. reported 13% SSI after hybrid revascularization¹⁵.

The 8.3% SSIs following (hybrid) femoral endarterectomy is among the lower ranges of that described in literature^{12,16,17}. A large percentage of SSIs was seen after endarterectomy coupled with peripheral angioplasty. An explanation for this could be found in the high percentage of diabetics in the group that underwent a peripheral hybrid procedure. The higher risk of infection that comes with diabetes, as well as the predominant pattern of distal arterial involvement of the tibial and peroneal arteries in patients with diabetes, could explain why these peripheral lesions are so prone to give rise to surgical site infections¹⁸. Hybrid procedures naturally had a longer duration of surgery, which is a known risk factor for SSI development. This alone cannot explain the higher proportion of SSI in the peripheral angioplasty group, since iliofemoral and peripheral hybrid procedures were comparable in duration of surgery, with the latter one being more prone to SSI development. Also, since Dosluoglu et al. reported lower SSI rates after hybrid surgery than following open endarterectomy, duration of surgery does not seem to be the most important factor in the development of SSI in these patients.

Patients who developed a SSI had a mean duration of 8 days longer than patients who had an uncomplicated recovery, due to prolonged administration of intravenous antibiotics as well as a higher number of reinterventions to control the infected area.

Among the limitations of this study are its retrospective nature, which may give rise to information bias. Another limitation is the small number of patients in the peripheral hybrid group, which makes it difficult to show significance in infection incidence between groups, especially with low overall infection rates. For further research on the safety and use of hybrid lower limb revascularization, a prospective trial focusing on SSI and patency could be considered.

To conclude, it can be said that the hybrid procedure combining open femoral endarterectomy combined with endovascular revascularization is a safe procedure without significant differences in infection rates between central or peripheral revascularization.

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5

Chapter 5

**Do surgical site infections in
open aortoiliac surgery differ
between occlusive and
aneurysmal arterial disease?**

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ABSTRACT

Background

Surgical site infections (SSI) are frequently seen after aortoiliac vascular surgery (2-14%). Deep SSIs are associated with graft infection, sepsis and mortality. This study evaluates the difference in incidence and nature of SSI following open aortoiliac surgery for aneurysmal disease compared to occlusive arterial disease.

Methods

A retrospective cohort study was conducted, including all consecutive patients who underwent open aortoiliac vascular surgery between January 2005 and December 2016 in the Amphia Hospital, Breda, The Netherlands. Patients were grouped by disease type, either aneurysmal or occlusive arterial disease. Data were gathered, including patient characteristics, potential risk factors and development of SSI. SSIs were defined in accordance with the criteria of the Centers for Disease Control.

Results

Between January 2005 and December 2016, 756 patients underwent open aortoiliac surgery, of which 517 had aortoiliac aneurysms and 225 had aortoiliac occlusive disease. The group with occlusive disease was younger, predominantly male and had more smokers. After exclusion of 228 patients undergoing acute surgery, the SSI rate after elective surgery was 6.2%, with 10 out of 301 SSIs in the aneurysmal group (3.0%) and 22 out of 213 SSIs in the group with occlusive disease (10.3%, $p < 0.001$). Also, infection-related readmission and re-intervention were higher after occlusive surgery, 6.6% vs 0.9% ($p < 0.001$) and 4.2% vs 0.9% ($p = 0.003$) respectively. *Staphylococcus aureus* was found as the most common pathogen, causing 64% of SSI in occlusive disease vs 10% in aneurysmal disease ($p = 0.005$). Logistic regression showed occlusive arterial disease and chronic renal disease were associated with SSI.

Conclusion

Our study presents evidence for a higher rate of SSI in patients with aortoiliac occlusive disease compared to aortoiliac aneurysmal disease, in part due to inherent use of inguinal incision in patients with occlusive disease. All precautions to prevent SSI should be taken in patients undergoing vascular surgery for arterial occlusive disease.

INTRODUCTION

Surgical site infections (SSI) are frequently seen after aortoiliac vascular surgery ¹. The reported incidence of SSI after open aortoiliac surgery varies between 2-14% for aneurysmal disease ²⁻⁵ and 4.6-7% for occlusive disease ⁶⁻⁸.

Where superficial surgical site infections cause morbidity and costs, deep SSI are associated with graft infection, re-intervention, sepsis and mortality. Prosthetic graft infection is a severe complication associated with high amputation rates (11%) and mortality varying between 20-40 % ⁹⁻¹². Recent research has shown a link between SSI and the development of aortic graft infection in abdominal aneurysm surgery ¹².

This study evaluates the incidence and nature of SSI following open aortoiliac surgery for either aneurysmal or occlusive arterial disease. Since occlusive arterial disease is related to microcirculatory dysfunction ¹³⁻¹⁵, it might have a negative impact on wound healing, and therefore the development of SSI. We hypothesize that, due to the different nature of aneurysmal and occlusive disease, patients who undergo aortoiliac surgery for occlusive disease have higher rates of SSI.

METHODS

Design

A retrospective analysis was conducted, including all patients who underwent open aortoiliac vascular surgery between January 2005 and December 2016 in the Amphia Hospital, a large teaching hospital in Breda, The Netherlands.

Patients and data collection

Patient data were gathered from a database of all patients undergoing aortoiliac surgery in the time period specified above. Patients who underwent open aortoiliac surgery for either arterial occlusive disease or aortoiliac aneurysmal disease were included. All endovascular surgery patients and patients who underwent surgery for aortoenteric fistulae or replacement of infected grafts were excluded. Mycotic aneurysms, while different in etiology, were included to assess the risk these aneurysms have on the development of SSI and graft infection.

Data were gathered by reviewing medical files in the hospital's electronic medical records. Patient characteristics included were age at the moment of surgery, sex, aneurysm location, aneurysm size at the moment of surgery, aneurysm morphology (mycotic or para-anastomotic), Fontaine stage, American Society of Anesthesiologists Physical Status

classification (ASA score) and specific risk factors such as smoking, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic renal disease (defined as an estimated glomerular filtration rate $<15\text{ml/min/1.73m}^2$), history of congestive heart failure and preoperative statin use. The postoperative information included type of procedure, duration of stay, time and number of re-interventions, mortality, and expansive information regarding surgical site infections. Acute surgery was scored when patients had a ruptured aneurysm or acute occlusion which required immediate surgical therapy.

SSIs were defined, in accordance with the criteria of the Centers for Disease Control ¹⁶, as the presence of heat, swelling or pain at or around the surgical site within 90 days after the initial procedure. They were categorized using the Szilagyi classification for vascular SSI ¹⁷. Szilagyi I is an infection confined to the dermis, Szilagyi II includes infections of the subcutaneous tissue, while Szilagyi III was scored when the infection affected the vascular graft. Dedicated and specifically trained infection control personnel performed scoring of SSI. The presence of an SSI was ascertained by a microbiologist and a vascular surgeon ¹⁸. Alternatively, a positive wound culture and/or drainage of pus from the wound or aspiration of pus in a diagnostic puncture were also criteria.

From February 2013 onwards, a protocol for *S. aureus* nasal screening was used in the research hospital ¹⁹. Following this protocol, all patients were subjected to nasal screening before vascular surgery. Patients who tested positive for *S. aureus* were subsequently treated with eradication therapy consisting of mupirocin ointment and chlorhexidine gluconate soap for 5 days before undergoing surgery.

Surgical procedures

All procedures were performed at the Amphia Hospital, Breda, The Netherlands in regular operating rooms. All patients received 2 grams of cefazolin as standard preoperative antibiotic prophylaxis.

Among the included procedures were aortic tube grafts, aortic bifurcation grafts (bilioaortic, bifemoral and combined), unilateral aortoiliac and aortofemoral bypass grafts, aortoiliac interposition grafts and aortoiliac endarterectomies.

Follow-up

Surgical sites were treated with a dry adhesive bandage for the first 48 hours after surgery. Transcutaneous stitches or staples, if used, were removed fourteen days after surgery.

All patients were followed up by clinical examination by a vascular surgeon on the outpatient clinic for a period of 3 months. Additional imaging was only performed upon suspicion of

complications. Patients were informed to contact a doctor immediately when signs of infection were present. All patients were followed for 1 year post surgery for mortality.

Statistical analysis

A Pearson χ^2 test was used to compare categorical variables; continuous variables were analysed using independent t-tests. Logistic regression was used to evaluate risk factors. Statistical analysis was performed using SPSS software v24.0 (SPSS Inc., Chicago, IL, USA). A P-value below 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

Between January 2005 and December 2016, 756 patients underwent open aortoiliac surgery. Fourteen patients were excluded due to a mix of occlusive and aneurysmal disease, aortoenteric fistulae or surgery for infected grafts. In addition, a total of 228 patients underwent acute surgery, 216 in the aneurysmal population, twelve in the occlusive group. These patients were excluded from further analysis. In the final analysis we included 301 with aortoiliac aneurysms and 213 with aortoiliac occlusive disease. The group with occlusive disease was younger (61.4 years SD 9.9 vs 70.4 years SD 6.9, $p<0.001$), had a higher ratio of smokers (67% vs 44%, $p<0.001$) and lower ratio of male patients (64% vs 81%, $p<0.001$). The baseline characteristics are displayed in full in table 1.

Surgical site infections

As shown in table 2, 32 (5.9%) patients developed a surgical site infection, with fifteen Szilagyí II infections affecting the subcutis and seven Szilagyí III infections affecting the vascular graft. Infections occurred in ten patients with aneurysmal disease (3.3%) and in 22 with occlusive disease (10.3%, $p=0.001$). Six Szilagyí II or III (2.0%) SSIs occurred in the aneurysmal group compared to sixteen (7.5%) in the occlusive group ($p=0.073$). There were more infection-related readmissions after surgery for occlusive disease (6.6%) compared to the aneurysmal group (1.0%, $p<0.001$), a difference that remained visible when corrected for patients who developed an SSI while still in the initial admission (8.5% in occlusive disease vs 2.7% in aneurysmal disease, $p=0.003$). Likewise, the occlusive group saw a higher number of patients who needed infection-related re-intervention (4.2% in occlusive disease vs 1.0% in aneurysmal disease, $p=0.017$). None of the SSIs in the aneurysm group were after surgery for mycotic aneurysm, although one patient with mycotic aneurysm died 4 months after initial surgery from anastomotic bleeding due to graft infection. No signs of SSI were seen in this patient during follow-up. One of four patients (25% vs 6.1% in patients without redo surgery,

p=0.227) with re-do surgery for occlusive arterial disease developed SSI (Szilagyi II, requiring surgical exploration).

Table 1. Patient characteristics in elective surgery

Characteristics	Aneurysmal (n=301)	Occlusive (n=213)	P-value
Mean age (SD)	70.4 (6.9)	61.4 (9.9)	<0.001
Sex, no. male (% male)	246 (81.7)	137 (64.3)	<0.001
ASA Score ≥ 3 (%)	148 (50.7)	120 (58.5)	0.084
Smoking (%)	129 (43.6)	143 (67.1)	<0.001
Diabetes mellitus (%)	56 (18.6)	41 (19.2)	0.854
Hypertension (%)	179 (59.5)	111 (52.1)	0.098
Chronic renal disease (%)	4 (1.3)	3 (1.4)	0.939
Lesion and surgical characteristics			
Aneurysm size in mm, mean (SD)	63.33 (12.7)		
Aneurysm Morphology (%)			
- Mycotic	8 (2.7)		
- Para-anastomotic	4 (1.3)		
Fontaine stage			
- 2a		10 (4.7)	
- 2b		113 (53.1)	
- 3		62 (29.1)	
- 4		28 (13.1)	
Surgical procedure (%)			
- Aortic tube graft	176 (58.5)	0	
- Aorto-iliac graft	90 (29.9)	47 (22.1)	
- Aorto-femoral graft	19 (6.3)	110 (51.6)	
- Aorto-iliofemoral graft	16 (5.3)	36 (16.9)	
- Ileo-femoral endarterectomy	0	15 (7.0)	
- Aortic endarterectomy	0	4 (1.9)	
- Axillofemoral bypass	0	1 (0.5)	
Inguinal incision*	49 (16.3)	177 (83.1)	<0.001
Re-do surgery within 1 year	0	4 (1.9)	0.029

*Including patients with more than one inguinal incision or inguinal incision combined with abdominal incision.

Table 2. Infection rates and secondary outcomes after elective surgery

	Aneurysmal (n=301)	Occlusive (n=213)	P-value
Surgical Site Infection rate (%)	10 (3.3)	22 (10.3)	0.001
Infection grade (%)			0.432
- Szilagyi I	4 (1.3)	6 (2.8)	
- Szilagyi II	3 (1.0)	12 (5.6)	
- Szilagyi III	3 (1.0)	4 (1.9)	
Time to infection in days, mean (SD)	22.6 (17.2)	19.4 (13.2)	0.388
Readmission for infection (%)	3 (1.0)	14 (6.6)	<0.001
- Including patients still admitted†	8 (2.7)	18 (8.5)	0.003
Re-intervention for infection (%)	3 (1.0)	9 (4.2)	0.017
Duration of hospital stay in days, mean (SD)*	13.02 (13.15)	10.09 (7.80)	0.021
30-day mortality (%)	15 (5.0)	5 (2.3)	0.128
6-month mortality (%)	22 (7.3)	10 (4.7)	0.227
1-year mortality (%)	25 (8.3)	11 (5.2)	0.169

*including duration of readmissions

† including patients who developed a SSI during the initial admission

Of 22 patients with Szilagyi II or III SSI (4.3% of all patients), eleven required short-term surgical re-intervention to control the infection. The other patients were treated with either outpatient exploration of the wound (7), radiographic drainage of a deeper abscess (1) or antibiotics only (3). One patient with Szilagyi I SSI required surgical re-intervention. One patient finally succumbed to progression of bowel ischemia.

The three re-interventions in the aneurysmal group all occurred after aortic tube graft surgery and were comprised of two drainages of intra-abdominal infected hematoma (of which one patient later developed multiple intra-abdominal abscesses) and one drainage of the inguinal wound which was used for femoral embolectomy the day after initial surgery. The nine re-interventions in the occlusive group developed after aortobifemoral graft (n=4) unilateral aortoiliac bypass (n=2), aortobiiliac graft (n=1), mixed aortofemoral and -iliac graft (n=1) and iliac endarterectomy (n=1). Therapy consisted of inguinal wound drainage (n=5), abdominal wound drainage (n=2), femorofemoral graft removal (n=1) and aortic bifurcation graft removal (n=1). One patient died of sepsis as a direct result of Szilagyi III SSI. Patients who developed a SSI had a longer duration of stay (mean 24.4 days, SD 28.1) than patients who did not (mean 11.0 days, SD 8.6; $p<0.001$). The mean time from initial surgery to infection did not differ significantly between groups (22.6 days for aneurysmal disease vs 19.4 days for occlusive disease, $p=0.563$).

As shown in table 1, patients with occlusive disease were more likely to get an inguinal incision. SSI occurred in 23 patients with inguinal incisions vs 9 patients without inguinal incision (10.2% vs 3.1%; $p=0.001$). 19 of these 23 (82.6%) infected inguinal incisions occurred in patients with occlusive disease ($p=0.013$). SSIs in inguinal incisions were not different in severity compared to non-inguinal incision SSIs (33.3% Szilagyi I in inguinal incision vs 30.4% Szilagyi I in other incisions; $p=0.983$). There was no significant difference in SSI in patients with higher Fontaine classification (8.9% in Fontaine 2, 12.9% in Fontaine 3, 10.7% in Fontaine 4; $p=0.70$).

Table 3 displays the distribution of infectious pathogens in patients with SSI. The majority (64%) of SSIs after surgery for occlusive disease tested positive for *Staphylococcus aureus*, compared to 10% of the SSIs after aneurysm surgery ($p=0.005$). There were no cases of Methicillin-resistant *S. aureus*. As stated in the methods section, a *S. aureus* screening protocol was used in the research hospital from February 2013 onwards. This screening data was only available for 66% of our study population. There was no difference in SSI incidence or Szilagyi type between patients positive or negative for *S. aureus* nasal screening ($p=0.140$).

Table 3. Infectious pathogens in patients with surgical site infection

	Aneurysmal (n=10)	Occlusive (n=22)	P-value
<i>Staphylococcus aureus</i>	1 (10)	14 (63.6)	0.005
<i>Escherichia coli</i>	2 (20)	-	NS
<i>Bacteroides fragilis</i>	1 (10)	1 (4.5)	NS
<i>Enterobacter cloacae</i>	-	3 (13.6)	NS
<i>Enterococcus faecalis</i>	1 (10)	-	NS
<i>Streptococcus anginosus</i>	2 (20)	-	NS
Coagulase-negative Staphylococci	-	2 (9.1)	NS
Group B streptococci	-	1 (4.5)	NS
No culture obtained	3 (30)	1 (4.5)	NS

NS: not significant

Univariate analysis revealed that higher age, kidney disease, inguinal incision and disease type affected the risk of surgical site infections. A logistic regression model was created to ascertain the effects of age, sex, incision location, disease type (occlusive of aneurysmal) and kidney disease on the likelihood of developing SSI.

As shown in table 4, patients with chronic renal disease were more likely to develop SSIs (OR 7.24, 95%CI 1.22-42.95, $p=0.029$). No significant effect was found for age, disease type or the use of an inguinal incision in this model.

Table 4. Determinants for surgical site infection in elective surgery with corresponding odds ratios (OR)

Covariate	Adjusted OR	95% Confidence Interval	P-value
Age	0.98	0.94-1.02	0.344
Smoking	0.54	0.25-1.17	0.117
Diabetes mellitus	0.88	0.33-2.31	0.787
Chronic renal disease	7.37	1.22-44.44	0.029
Aortoiliac occlusive disease	1.89	0.62-5.76	0.264
Inguinal incision	2.30	0.81-6.58	0.119

Secondary outcomes

Both 30-day mortality (5.5% vs 2.3%, $p=0.085$) and 1-year mortality (8.8% vs 5.2%, $p=0.115$) were higher in the aneurysmal group, this was not statistically significant. Although fewer infections occurred in the aneurysmal group, the mean duration of stay for this group was significantly longer (13.1 days, SD 12.9; vs 10.1 days, SD 7.8; $p=0.003$).

DISCUSSION

Outcomes

Patients undergoing open aortoiliac surgery for occlusive vascular disease have a higher risk of developing SSI than patients with aneurysmal disease. Though more infections occurred after surgery for occlusive rather than aneurysmal disease, the consequences of the infections were similar. Both groups saw similar rates of readmissions and re-interventions for SSIs. Mortality was higher in the aneurysmal group, but this is likely explained by the 10 years' average age difference between the groups. This could also cause the longer duration of stay for the aneurysmal group, despite there being fewer infections among these patients.

The overall infection rate after open aortoiliac surgery was comparable to the 0.5-14% incidence rate reported in literature ²⁻⁵. However, the incidence (10.3 %) of SSI after surgery for occlusive disease was higher than described in the literature (4.6-7%), but this comparison may be flawed as these studies used either laparoscopic techniques, or only aortobifemoral grafts, where our study included all operations in the aortoiliac region ⁶⁻⁸. To our knowledge, this is the first report to compare the rate and characteristics of surgical site infections between patients with aortoiliac aneurysmal disease and aortoiliac occlusive disease. We found a disparity in the incidence of SSI between the groups, with more SSIs developing in patients with occlusive disease. One reason for this difference might be the frequent use of

inguinal incisions, a known risk factor for SSI development ². The inguinal region is higher in temperature and humidity, which encourages the growth of microorganisms that thrive in moist conditions, which might explain the higher number of SSIs in inguinal incisions ^{20,21}. Our analysis showed strong collinearity between occlusive arterial disease and the use of inguinal surgical access, meaning the risk of inguinal incisions may be inherent to the surgical treatment of occlusive arterial disease. As most patients with aortoiliac occlusive disease cannot be treated without an inguinal incision, this incision should be treated as an inevitable part of the treatment instead of an independent risk factor. This does mean, however, that patients with occlusive arterial disease should be seen as a high-risk group for SSI, and every precaution should be taken to prevent postoperative infection. This should always include following the Global Guidelines for the Prevention of Surgical Site Infection by the WHO ²². It could further include preventing the use of inguinal incisions, using negative pressure wound therapy, smoking cessation prior to surgery and a critical review of which patients require high-risk procedures. Over half of patients with occlusive disease in our study were treated for Fontaine 2 disease, patients who do not require immediate limb-saving surgery. Shared decision making should be applied while counselling these patients before surgery keeping high SSI risk in mind.

Another explanation for the higher SSI rate in occlusive arterial disease is the pathophysiological difference between the conditions. Occlusive arterial disease is characterized by plaque build-up through atherosclerosis, which, when present in the aortoiliac region, is what eventually causes intermittent claudication or critical ischemia due to insufficient blood supply for tissues distal to the lesion. This vessel disease is not limited to the larger arteries, but affects arterioles and capillaries as well. Common risk factors for arterial occlusive disease such as age, diabetes mellitus, smoking and dyslipidaemia are all associated with decreased tissue perfusion ²³⁻²⁶ and the association between microcirculatory dysfunction and occlusive arterial disease has been shown previously ¹³⁻¹⁵. Since proper microcirculation is a prerequisite for decent wound healing ²⁷, one might assume that the nature of arterial occlusive disease is the underlying cause of the higher rate of surgical site infections.

Staphylococcus aureus was the most frequently found causative agent for SSI, with 14 out of 15 *S. aureus*-infections in patients with occlusive disease. Previous studies show that a reduction in *S. aureus*-infections might be accomplished in open aortoiliac surgery by means of specific eradication therapy for nasal carriers, which was associated with a significant reduction in 1-year mortality ^{19,28}. Graft infection with *S. aureus* occurs in less than 1% of aortic grafts and in 2-5% of inguinal grafts, with associated mortality and major amputations as high as 40%. It seems that especially in patients with aortoiliac occlusive disease, a large amount of *S. aureus*-related mortality and morbidity can be prevented.

Graft infections

While our data was not sufficient to provide complete follow-up data of graft infections, earlier research shows that SSI is a risk factor for the development of aortic graft infection^{12,29}. The vast majority (96%) of our study population was treated with bypass grafting. The literature reports overall incidences of graft infection between 0.6-3.0%, and up to 4.3% after open reconstructive graft surgery for aneurysmal disease^{12,30-33}. If these numbers can be extrapolated, we expect an even higher incidence of graft infections in the long-term follow-up of open bypass surgery in aortoiliac occlusive disease, due to the higher incidence of SSI in this group. In agreement with other studies¹, the duration of hospital stay was significantly longer for patients who developed a SSI. While a cost-benefit analysis was not conducted, it is apparent that the longer admission (on average more than 13 days longer) leads to increased health care costs. Therefore, interventions that prevent the occurrence of SSI are likely to be cost-effective.

Limitations

The retrospective nature of our research is a cause for potential bias. Some data were more than 10 years old and were therefore gathered from summarized medical patient information. Other data, like patient body mass index (BMI), length of surgery, administration of blood transfusion, intra-operative normothermia, peri-operative blood glucose control and hypoalbuminemia could not be reliably retrieved.

Infections were only counted when they fulfilled the criteria that we set out above. Consequently, the limited available information might be cause for an underestimation of the total number of surgical site infections. Also, due to the comparison between two different disease types, inherent differences between the aneurysmal and occlusive patient population exist. Patients with aneurysmal disease were on average 10 years older, which might explain the higher mortality. The effect of age on mortality in our group was confirmed by logistic regression. As mentioned above, due to the nature of the disease, the surgical procedures varied between groups, leading to a higher rate of inguinal incisions used in patients with occlusive arterial disease.

CONCLUSION

Our study presents evidence for a higher rate of SSI in patients with aortoiliac occlusive disease compared to aortoiliac aneurysmal disease, in part due to inherent use of inguinal incision in patients with occlusive disease. All precautions to prevent SSI should be taken in patients undergoing vascular surgery for arterial occlusive disease.

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6

Chapter 6

Surgical Site and Graft Infections in Endovascular and Open Abdominal Aortic Aneurysm Surgery

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ABSTRACT

Background

Surgical site infections (SSIs) constitute one of many major complications after aortic aneurysm surgery and its details and outcome have not been evaluated extensively. This research evaluates the incidence and outcome of SSI and graft infection in open and endovascular abdominal aortic aneurysm surgery.

Patients and Methods

A retrospective study was performed, including all patients who underwent surgery for aortoiliac aneurysmal disease between January 2000 and December 2016 in the Amphia Hospital, Breda, The Netherlands. Surgical site infections were defined in accordance with criteria of the U.S. Centers for Disease Control and Prevention (CDC). Aortic graft infection was diagnosed by a combination of computed tomography imaging and microbiologic results.

Results

Between January 2000 and December 2016, 845 patients (mean age, 72.80 – 7.15 y, 86.3% male) underwent abdominal aneurysm surgery (477 endovascular, 368 open). The total SSI rate was 3.1% (12 endovascular [2.5%], 14 open [3.8%], $p = 0.318$) with 0.8% deep SSI (26.9% of SSIs). No difference in SSIs was found between acute and elective surgery (2.9% vs. 3.1%, $p = 1.000$). Patients with SSI had a longer duration of stay (mean, 27.65 – 30.74 d vs. 9.79 – 12.50 d, $p < 0.0001$) but no difference in 30-day or 1-year mortality. Twenty-four graft infections occurred (4.3% of open vs. 1.7% of endovascular surgery, $p = 0.023$) of which 20 (83.3%) required surgery. Two-year mortality was higher when graft infections occurred (33.3% vs. 16.3%, $p = 0.046$). Surgical site infections (odds ratio [OR] 7.10, 95% [CI] 2.10–23.98) and mycotic aneurysms (OR 9.38, 95% CI 1.78–54.19) are independent determinants for graft infections.

Conclusion

This study shows that SSIs after endovascular aortic surgery are as common as after open aortic surgery. Furthermore, this study supports the concept that aortic graft infection is highly associated with SSIs and mycotic aneurysms. Studies evaluating the prevention or early diagnosis of graft infection after SSIs through intensified imaging follow-up or even long-term antibiotic treatment should be considered.

INTRODUCTION

Infections are major complications after aortic aneurysm surgery ¹. The incidence of surgical site infections (SSIs) is reported to be between 0.5% and 1.5% for endovascular surgery and between 2% and 14% for open surgery ²⁻⁵. Most studies that describe SSIs after abdominal aortic aneurysm surgery only report incidence numbers, without providing details of cause and outcome after SSIs. We hypothesize that the incidence of SSIs in endovascular aortic aneurysm surgery (EVAR) is higher than reported in the literature.

Deep SSIs are associated with aortic graft infection, sepsis, aortic rupture, and early mortality. Prosthetic aortic graft infection is a severe complication after open and endovascular abdominal aneurysm surgery with a mortality rate of 20%–40%, often requiring surgical intervention, with high amputation rates of 11% ⁶⁻⁸. Trends have been reported suggesting a link between perioperative infections and the development of aortic graft infection ⁹, although no conclusive evidence can be found.

This research evaluates the incidence of SSIs and graft infection in open and endovascular abdominal aortic aneurysm surgery. It also reports the outcome of patients who develop an SSI or graft infection after abdominal aneurysm surgery.

PATIENTS AND METHODS

Design

A retrospective study was conducted, including all patients who underwent surgery for aortoiliac aneurysmal disease between January 2000 and December 2016 in the Amphia Hospital, Breda, The Netherlands.

Patients and data collection

Patient data were gathered from a database of all patients undergoing aortoiliac surgery in the aforementioned timeframe, selecting the patients with aneurysmal disease, rather than occlusive aortoiliac disease. Both endovascular and open surgical procedures were included. Data were gathered retrospectively by reviewing medical files in the hospital's electronic medical record. Patient characteristics included were age at the time of surgery, gender, aneurysm location, aneurysm size at the time of surgery, aneurysm morphology (mycotic, saccular, or paraanastomotic), American Society of Anesthesiologists Physical Status classification (ASA score), and specific risk factors such as smoking, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic renal disease, history of congestive heart failure, and pre-operative statin use. The post-operative information included duration of stay, time and number of re-interventions, pulmonary infections, urinary

tract infections, bowel ischemia, and expansive information regarding SSIs, and graft infections. Surgical site infections were defined, in accordance with the criteria of the U.S.

Centers for Disease Control and Prevention (CDC) ¹⁰, as the presence of heat, swelling, or pain at or around the surgical site within 90 days after the initial procedure. Alternatively, a positive incision culture and/or drainage of pus from the incision or aspiration of pus in a diagnostic puncture were also criteria. Aortic graft infection was diagnosed by a combination of positron emission tomography or computed tomography imaging and positive blood culture or a culture from the graft during surgery.

Surgical procedures

All procedures were performed at the Amphia Hospital, Breda, The Netherlands. A regular operating room was used for both endovascular and open surgery, using a mobile C-arm for imaging support for endovascular operations. All EVAR procedures were performed using open surgical access to both femoral arteries. All patients received two grams of cefazolin as standard pre-operative antibiotic prophylaxis. The choice for endovascular or open treatment and choice of (endo)graft type were made by the treating physician based on patient age, comorbidities, and aneurysm morphology. Acute surgery was scored when patients had a ruptured aneurysm at the time of surgery. Symptomatic aneurysm was scored when patients received aneurysm surgery within 24 hours of emergency admittance as a result of suspicion of symptomatic aneurysm through abdominal or flank pain, thromboembolism, and some cases of mycotic aneurysm. Open acute surgery constituted of either aortic tube or aortic bifurcation implantation. Endovascular acute surgery was performed by unilateral iliacal stenting with surgically implanted femorofemoral crossover. Among endovascular grafts used were Cook Zenith (Cook Medical LLC, Bloomington, IN), Gore Excluder (W. L. Gore & Associates, Inc., Flagstaff, AZ), Endologix AFX and Nellix (Endologix Inc., Irvine, CA), and Medtronic Endurant (Medtronic Minneapolis, MN).

Follow-up

Surgical sites were treated with a dry adhesive bandage for the first 48 hours after surgery. Transcutaneous stitches or staples, if used, were removed 14 days after surgery. All patients were followed up by clinical examination by a vascular surgeon on the outpatient clinic for a period of three months. Additional imaging was only performed upon suspicion of complications. Patients were informed to contact a doctor immediately when signs of infection were present. Loss to follow-up was scored after a patient was not seen in our hospital for a period longer than 24 months, except in the case of patient death. The last patient visit was extracted from our hospital's electronic patient records.

Statistical analysis

A Pearson χ^2 test was used to compare categorical variables; continuous variables were analyzed using independent t-tests. Logistic regression was used to evaluate risk factors. Statistical analysis was performed using SPSS software v24.0 (SPSS Inc., Chicago, IL). P values used were two-sided, unless explicitly mentioned as one-sided. A p value below 0.05 (or a one-sided p value below 0.025) indicated statistical significance.

RESULTS

Between January 2000 and December 2016, 845 patients underwent aortoiliac aneurysm surgery. Endovascular procedures accounted for 477 cases, of which 412 (86.4%) were elective procedures. A total of 368 patients underwent open surgery, of which 224 (60.9%) procedures were elective. The baseline characteristics are shown in Table 1. The ratio of male patients was significantly higher in the endovascular group, whereas substantially more iliac aneurysms were treated with open procedures. The mean aneurysm diameter at surgery was higher in the group of patients treated with open surgery. Endovascular procedures were performed using Medtronic Endurant (n = 332), Gore Excluder (n = 20), Cook Zenith (n = 121), Endologix AFX (n = 1), and Endologix Nellix (n = 1). Two device brands could not be recovered from medical records. A mean follow-up duration of 49 months was observed, with 20 (2.37%) patients lost to follow-up.

Surgical site infections

A total of 26 (3.1%) SSIs occurred, of which eight were after acute surgery (Table 2). After elective surgery, 11 endovascular surgery patients (2.7%) and nine open surgery patients (4.0%) developed an SSI ($p = 0.352$), as shown in Table 3. Of these, three (0.5%) deep SSIs occurred after endovascular treatment and three (1.3%) deep SSIs occurred after open abdominal access ($p = 0.351$). Table 4 presents the outcome after acute surgery. After acute surgery for ruptured or symptomatic abdominal aneurysm, one (1.5%) SSI occurred after endovascular treatment and five (3.5%) after open treatment ($p = 0.668$). All infections after acute endovascular procedures were deep infections, compared with one-fourth (1; 0.7%) of the infections after acute open surgery. All but one patient were treated with antibiotic agents after diagnosis of the SSI. This patient underwent incision and drainage of the surgical site abscess without further antibiotic treatment. All seven (0.8% of all) patients with deep SSIs required short-term surgery for infection control. Four patients required surgical evacuation of infected hematoma, one patient required drainage of abdominal abscesses that had contributed to abdominal evisceration. Removal of the prosthesis was necessary in two patients, in whom the synthetic femorofemoral crossovers were replaced with venous crossovers. One patient died as a direct consequence of deep SSI.

The mean hospital duration of stay was longer for patients with SSIs (9.79 – 12.50 d without SSI vs. 27.65 – 30.74 d with c SSI; $p < 0.0001$). Table 5 presents the outcomes grouped for patients with SSI.

Table 1. Patient characteristics

Characteristics	Endovascular (n=477)	Open (n=368)	P-value
Mean (SD) age	73.82 (7.06)	71.47 (7.06)	<0.0001
Sex, no. male (% male)	423 (88.7)	306 (83.2)	0.026
ASA Score ≥ 3 (%)	286 (61.5)	222 (64.7)	0.377
Smoking (%)	153 (32.1)	157 (42.9)	0.002
Diabetes mellitus (%)	81 (17.0)	59 (16.0)	0.780
Hypertension (%)	269 (56.8)	212 (59.6)	0.435
Chronic renal disease (%)	19 (4.1)	21 (5.8)	0.327
Cardiac history (%)	218 (45.9)	139 (39.3)	0.065
Ruptured aneurysm (%)	45 (9.4)	125 (34.0)	<0.0001
Aneurysm Characteristics			
Mean (SD) aneurysm diameter in mm	62.99 (11.98)	70.31 (17.31)	<0.0001
Mycotic (%)	3 (0.6)	9 (2.5)	0.037
Anastomotic (%)	6 (1.3)	3 (0.8)	0.432
Saccular (%)	6 (1.3)	1 (0.3)	0.081
Iliac aneurysm (%)	34 (7.1)	55 (14.9)	<0.0001

Table 2. Overall infection rates and secondary outcomes

	Endovascular (n= 477)	Open (n=368)	P-value
Surgical Site Infection rate (%)	12 (2.5)	14 (3.8)	0.318
- Superficial infection (%)	9 (1.9)	10 (2.7)	0.477
- Deep infection (%)	3 (0.6)	4 (1.1)	
Readmission for infection (%)	9 (1.9)	5 (1.4)	0.599
Re-intervention for infection (%)	4 (0.8)	4 (1.1)	0.734
Duration of hospital stay (mean, SD)*	6.55 (7.56)	15.26 (17.83)	<0.0001
30-day mortality (%)	15 (3.1)	47 (12.8)	<0.0001
6 month mortality (%)	31 (6.5)	65 (17.7)	<0.0001
1 year mortality (%)	40 (8.4)	69 (18.8)	<0.0001

*including duration of readmissions

Table 3. Infection rates and secondary outcomes after elective surgery

	Endovascular (n= 412)	Open (n=224)	P-value
Surgical Site Infection rate (%)	11 (2.7)	9 (4.0)	0.352
- Superficial infection (%)	9 (2.2)	6 (2.7)	0.351
- Deep infection (%)	2 (0.5)	3 (1.3)	
Readmission for infection (%)	8 (1.9)	4 (1.8)	1.000
Re-intervention for infection (%)	3 (0.7)	4 (1.8)	0.357
Duration of hospital stay (mean, SD)*	5.96 (7.19)	13.86 (14.76)	<0.0001
Re-intervention within 30 days	22 (5.3)	32 (14.3)	<0.0001
Re-intervention within 1 year	46 (11.2)	43 (19.2)	0.008
30-day mortality (%)	4 (1.0)	11 (4.9)	0.004
6 month mortality (%)	18 (4.4)	16 (7.1)	0.144
1 year mortality (%)	24 (5.8)	19 (8.5)	0.247

*including duration of readmissions

Table 4. Infection rates and secondary outcomes in acute surgery

	Endovascular (n= 65)		Open (n=144)		P-value
	Rupture (n=45)	Symptomatic (n=20)	Rupture (n=125)	Symptomatic (n=19)	
Surgical Site Infection rate (%)	1 (1.5)	0	5 (3.5)	0	0.668
- Superficial infection (%)	0	0	3 (2.1)	0	0.526
- Deep infection (%)	1 (1.5)	0	2 (1.4)	0	
Readmission for infection (%)	1 (1.5)	0	1 (0.7)	0	0.526
Re-intervention for infection (%)	1 (1.5)	0	1 (1.5)	0	0.526
Duration of hospital stay (mean, SD)*	10.8 (8.1)	6.6 (3.5)	18.5 (22.8)	10.4 (7.5)	0.011
30-day mortality (%)	10 (15.4)	1 (1.5)	33 (22.9)	3 (2.1)	0.215
6 month mortality (%)	12 (18.5)	1 (1.5)	46 (31.9)	3 (2.1)	0.049
1 year mortality (%)	14 (21.5)	2 (3.0)	47 (32.6)	3 (2.1)	0.153

*including duration of readmissions

In 10 patients with SSIs, wound cultures yielded *Staphylococcus aureus* as the infectious pathogen. Three surgical site swabs tested positive for *Streptococcus epidermidis*, two for *Bacteroides fragilis*, and two for *Escherichia coli*. *Pseudomonas aeruginosa*, *Morganella morganii*, undetermined coagulase-negative staphylococci, and otherwise unspecified gram-positive rods were all isolated once, from different sites. Two cultures yielded mixed flora and in three patients a positive culture was not obtained. The mean time to infection was 22 days (range, 5–65). This duration did not differ between elective and acute surgery (mean, 21.8 – 14.8 vs. mean, 27.5 – 17.9; $p = 0.434$) or endovascular and open surgery (mean, 21.1 – 12.6 vs. mean, 24.8 – 17.8; $p = 0.552$). A logistic regression revealed no independent risk factor for developing surgical site infections. A Mantel-Cox log rank test showed a one-year mortality of 12.8% without SSI versus 15.4% with SSI with a p -value of 0.657.

Table 5. Characteristics and outcome by surgical site infection.

	With SSI (n=26)	Without SSI (n=819)	P-value
Mean duration of hospital stay (SD)	27.65 (30.74)	9.79 (12.50)	<0.0001
Re-intervention <30 days (%)	9 (34.6)	91 (11.1)	0.002
Re-intervention <1 year (%)	11 (42.3)	135 (16.5)	0.002
30-day mortality	1 (3.8)	61 (7.4)	0.714
6-month mortality	3 (11.5)	93 (11.4)	1.000
Graft infection	4 (15.4)	20 (2.4)	0.005

Graft infections

A total of 24 (2.8%) graft infections occurred, 16 open reconstructive grafts (4.3% of all open grafts) and eight endografts (1.7% of endovascular grafts, $p = 0.023$). All cases were diagnosed by a combination of positive blood culture and radiographic imaging. The mean time to graft infection was 392 days (–696; range, 12–3,289) with a median of 118 days. Surgery was required in 20 (83.3%) patients with graft infection, although five of them died before surgery or were deemed inoperable because of rapid decline. Of 15 operations, 11 consisted of open graft replacement, with nine rifampicin-soaked graft replacements, one autologous aortibifurcation replacement using the superficial femoral vein, and one autologous venous replacement of a femorofemoral crossover. Three of these removed grafts were endografts after EVAR, constituting 0.6% of all endovascular treatments, compared with eight (2.2%) graft removals after open surgery ($p = 0.066$). The remaining four procedures were because of bleeding from infectious pseudo-aneurysm ($n = 3$) and drainage of abdominal abscesses and evisceration treatment ($n = 1$). Patients with graft infections were treated with antibiotic agents for an average of 325 days, ranging from 0 to 2,447 days. When discarding the extremes, such as three patients who were put on life-long antibiotic treatment and three patients who died within a week of being diagnosed with graft infection, patients

were treated for a mean of 138 days, ranging from 14 to 440 days. The choice for the length of antibiotic treatment was made by the treating physician and clinical microbiologist based on the patient's symptoms, infectious pathogen, radiographic imaging, and laboratory tests. The 30-day mortality for patients with graft infections was not significantly different from patients without graft infection (3.7% vs. 7.5%, $p = 0.714$). Over time, however, a difference is revealed with 25.0% one-year mortality for infected grafts versus 12.5% for grafts free of infection ($p = 0.111$). It becomes even more distinct two years after surgery, seen in a two-year mortality of 33.3% after graft infection, compared with 16.3% without infection ($p = 0.046$). Ten patients (41.7% of patients with graft infection) died as a direct consequence of the graft infection.

A logistic regression revealed that patients who develop an SSI (both superficial and deep) are 7.1 (95% CI 2.1–24.0) times more likely to develop a graft infection ($p < 0.0001$). The complete results from the logistic regression are shown in Table 6.

A striking, although perhaps not surprising find was the high percentage of graft infections after surgery for suspected mycotic aneurysms (OR 7.71, $p = 0.011$). Two of 12 patients with mycotic aneurysm surgery developed a graft infection despite rigorous post-operative antibiotic treatment.

Table 6. Determinants for graft infection with corresponding odds ratios (OR)

Covariate	Adjusted OR	95% Confidence Interval
Surgical Site Infection	7.10	2.10 – 23.98
Endovascular Surgery	0.62	0.24 – 1.65
Mycotic Aneurysm	9.83	1.78 – 54.19
Diabetes Mellitus	1.18	0.38 – 3.70
Smoking	1.54	0.65 – 3.64
Ruptured Aneurysm	0.97	0.36 – 2.59
Pulmonary infection <30 days of surgery	2.91	1.01 – 8.39

Secondary outcomes

Limiting the analysis to elective surgery, there were more overall re-interventions within 30 days of surgery after open surgery than after endovascular surgery (14.3% vs. 5.3%, $p < 0.0001$). This difference in re-interventions was also present after one year (19.2% vs. 11.2%, $p = 0.008$). The 30-day mortality after elective surgery was 1.0% for endovascular surgery versus 4.9% for open surgery ($p = 0.004$). This difference dissipated over the months, with 4.4% versus 7.1% ($p = 0.144$) after six months and 5.8% versus 8.5% ($p = 0.247$) after one year.

After acute surgery, the rate of re-intervention within 30 days was 20.0% after endovascular surgery and 27.2% after open surgery ($p = 0.425$). After one year, this difference disappeared with 31.1% after endovascular treatment versus 30.4% after open surgery ($p = 1.000$). The 30-day mortality after endovascular intervention for ruptured aneurysm was 22.2%, opposed to 26.4% after open aneurysm repair ($p = 0.691$). One-year mortality in this group was 31.1% for endovascular surgery versus 37.6% after open treatment ($p = 0.474$).

DISCUSSION

To our knowledge, this is the first study giving an in-depth report of SSIs after abdominal aortic aneurysm surgery. Most studies report incidence numbers (between 0.5% and 14%) but do not describe the effects and outcome of SSIs ^{3–5,11,12}. Our study shows that with an incidence of 3.4%, SSIs are a relatively frequent complication with serious consequences. In our population, contrary to findings in the literature ^{4,5}, SSI after endovascular aortic aneurysm repair is as prevalent as SSI after open aortic aneurysm surgery. Deep SSIs warrant major surgery in more than 90% of cases and are associated with a mortality of 28%. This corresponds with findings in the literature ⁸. As other studies have shown ¹, the duration of hospital stay is longer for patients developing SSIs. Although we did not conduct a cost-benefit analysis, it is clear that the longer hospital stay (on average more than 18 days longer) leads to increased healthcare costs.

Potential bias of this study lies in the retrospective nature of the research. Some data accessed were more than 10 years old and had to be gathered from minimal or brief patient information. This might be cause for an underestimation of the found number of SSIs. Also, the comparison between open and endovascular procedure may be biased by the indication for one or the other procedure. For instance, while emergency endovascular aorta repair is increasing, in this cohort the majority of ruptured aneurysms were treated with open abdominal surgery. One-third of all open surgeries were because of ruptured aneurysm, compared with only 10% acute surgery in the endovascular group. Furthermore, there are certain patient characteristics that may sway the choice toward open or endovascular treatment.

Endovascular aorta repair is characterized by both frequent and long-term imaging follow-up for early endoleak diagnosis. Therefore, an otherwise healthy 50-year-old patient could be treated better with open surgery to prevent a high follow-up burden for the patient. Conversely, an older patient with considerable comorbidities might be better off undergoing a less invasive endovascular repair, which is known to have lower short-term mortality ¹³. Last, regardless of patient age or comorbidity, some aneurysms have a morphology poorly suited for endoluminal stenting, ruling out these patients for endovascular surgery altogether. Because the indications for these two types of surgery may vary, some outcome measures are

influenced by the choice of treatment. Ruptured aneurysms are associated with high 30-day (18%–35% for endovascular and 24%–37% for open treatment) and one-year mortality (37% for endovascular and 45% open treatment) ¹⁴. This might explain the difference in mortality between the two groups in this study.

The incidence of graft infections corresponds with the range of 0.6%–3.0% reported in the literature ^{15–17}. In accordance with Vogel et al. ⁹, we find that SSI is a risk factor for development of aortic graft infection. In addition to SSI, mycotic aneurysm was an independent risk factor for developing a graft infection, and a trend was seen for pulmonary infection within 30 days of surgery, although this was not significant. Although it seems intuitive that patients with peri-operative infectious disease have a higher risk for graft infections, these are also the patients who are rigorously treated with antibiotic agents. This would mean that the antibiotic treatment that suffices for treating SSI or pulmonary infection is insufficiently adequate in preventing bacteremia or the bacterial colonization of the graft. It might be worth investigating whether routine long-term antibiotic prophylaxis in patients with a mycotic aneurysm or an SSI after aortic graft surgery reduces the risk of aortic graft infection. Another, less invasive option would be to subject patients who develop an SSI after aortic graft implantation to intensified follow-up with more frequent radiographic imaging. We suggest that this follow-up period should constitute at least the first year after surgery, because 70% of graft infections occurred within one year.

As mentioned above, most SSIs were caused by *Staphylococcus aureus*. Previous studies show a reduction in one year mortality after decreased amounts of *Staphylococcus aureus* SSI ¹⁸. Our recent research has shown that SSIs with *Staphylococcus aureus* can be prevented in nasal carriers undergoing aortoiliac surgery by means of eradication therapy ². This could mean that by preventing *Staphylococcus aureus* SSIs, considerable amounts of subsequent graft infections could be avoided.

CONCLUSION

This study shows that SSIs after endovascular aortic surgery are as common as after open aortic surgery and are highly associated with graft infection. Also, patients with a primary mycotic aneurysm were at risk for developing graft infection. Studies evaluating the prevention or early diagnosis of graft infection after SSIs through intensified imaging follow-up or even long-term antibiotic treatment should be considered.

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7

Chapter 7

**Summary, general discussion
and future aspects**

Prevention of surgical site infections in vascular surgery

Staphylococcus aureus nasal carriage increases the risk for the development of SSI ¹⁻⁴. This risk can be reduced by preoperative screening and eradication treatment using mupirocin and chlorhexidine, as shown in multiple surgery populations ⁵⁻⁷. The effectiveness of preoperative screening and eradication therapy in the prevention of SSI in vascular surgery has not been established. **Chapter 2** evaluated the relation between *S. aureus* eradication therapy and SSI in a vascular surgery population. By comparing two *S. aureus*-positive cohorts of which one was treated with eradication therapy, a reduction in *S. aureus* infection from 5 out of 51 (9.8%) to 3 out of 104 infections (2.2%; 95% confidence interval 0.02-1.39; $P = 0.13$). A trend was seen towards effectiveness in aortoiliac surgery, with 3 out of 23 (13.0%) infections in the control group vs 0 out of 44 in the intervention group ($P = 0.074$). No effect was found in patients undergoing peripheral vascular surgery, with 2 out of 28 patients (7.1%) in the control group vs 3 out of 60 (5.0%) patients in the intervention group developing *S. aureus* SSI ($P = 0.651$). A possible reason for this difference in effect of treatment is the higher prevalence of leg ulcers in the peripheral surgery group before and during the surgical procedure. These ulcers may often be polymicrobially infected with gram positive cocci, gram negative rods and anaerobic organisms, which may easily spread to the surgical incision site in the groin area of the affected leg ⁸. Another explanation for the lack of reduction of SSIs in treated *S. aureus*-carriers who undergo peripheral surgery is the implementation of a bundle of care in the Amphia Hospital shortly before the study period. This bundle of care, which was implemented to reduce SSIs, lowered the incidence of SSIs in patients who underwent vascular surgery by 44% in two years' time (from 14.9% to 8.4%) ⁹. A further reduction of this already low prevalence of infections might be hard to achieve and is certainly hard to prove. An alternative explanation is that among the patients undergoing aortoiliac surgery were patients who underwent EVAR, which has a lower SSI risk than open aneurysm repair.

Chapter 3 showed the efficacy of eradication therapy on an expanded cohort of aortoiliac surgery patients. It showed a reduction in *S. aureus* infection from 13.6% to 0 ($P = 0.010$) with lower thirty-day mortality (1.3% vs. 13.6%, $P = 0.035$) and a lower rate of re-interventions (12.0% vs. 31.8%, $P = 0.046$). The effect found in the study population is comparable to previous studies on *S. aureus* eradication in non-vascular surgery and underwrites the conditional recommendation by the *World Health Organization's Global Guidelines for the Prevention of Surgical Site Infection* to treat surgery patients with perioperative intranasal mupirocin ¹⁰⁻¹². Besides reducing mortality, eradication treatment has also shown to reduce hospital costs substantially. On average, €1911 per patient was saved when treated with eradication therapy compared to placebo ¹³. Cost-effectiveness has not been evaluated in a vascular surgery population. Arguably, costs could be further reduced by treating patients regardless of nasal carriage, thus omitting the screening. However, with growing antimicrobial resistance, we believe it is unethical and potentially harmful to provide

a high number of patients with a treatment that may increase antibiotic resistance that might have no beneficial effect in non-colonized patients.

Risk factors for surgical site infections in vascular surgery

PAD frequently combines iliac or popliteal lesions with stenosis or occlusions of the common femoral artery. Since common femoral artery lesions are difficult to treat with endovascular procedures, multi-level occlusive lesions need multiple approaches. Hybrid revascularization combines open common femoral artery endarterectomy (CFE) with endovascular angioplasty and/or stenting to treat multi-level PAD in a single procedure. This appears to be safe and less invasive, despite longer operating sessions¹⁴⁻¹⁶. **Chapter 4** assessed the impact of SSI following CFE and hybrid procedures in a large teaching hospital. The study displayed an overall SSI rate of 8.3%, which is low compared to the rates ranging from 13%-15.4% in the literature¹⁷⁻²¹. A trend was observed towards more SSIs in peripheral hybrid procedures (12.5%), compared to aortoiliac hybrid (7.7%) or CFE-only interventions (7.6%, $P = 0.08$). Likewise, peripheral hybrid surgery had a higher chance of infection related re-intervention (6.3%) compared to iliac hybrid (1.5%) and CFE-only (1.5%, $P = 0.24$). Logistic regression showed an inclination toward diabetes mellitus as a determinant for SSI development (Odds ratio [OR] 2.68, 95% confidence interval [CI] 0.98 – 7.33, $P = 0.055$). This may explain the higher risk for SSI in peripheral procedures, since diabetes in PAD is often accompanied by distal arterial lesions, like the tibial and peroneal arteries²². Cost analysis comparing staged hybrid procedures and simultaneous hybrid procedures show reduced costs for simultaneous revascularization²³. A United States study found a mean cost of US\$ 45,654 for same-day hybrid and US\$ 73,851 for staged hybrid procedures ($P < 0.0001$) with a mean length of stay of 4.4 days in simultaneous vs. 9.2 days in staged interventions ($P < 0.0001$). These results only partially apply to our study, since it reported on hybrid procedures including CFE, lower extremity bypass graft and aortoiliac bypass graft rather than only CFE in chapter 4. Despite showing that hybrid surgery with bypass grafts costs more than hybrid surgery with CFE, CFE-based hybrid revascularization is more cost-effective than staged hybrid surgery²³. The same study showed diabetes in hybrid revascularization to increase costs (OR 0.94, 95% CI 0.87-1.01, $P = 0.088$) and length of stay (OR 0.92, 95% CI 0.84-1.0, $P = 0.051$). Despite being more cost-effective than two separate procedures, hybrid revascularization is more patient-friendly due to the comfort of only having to undergo one surgical session, combined with shorter hospital stay.

SSIs are frequently present after open aortoiliac surgery²⁴, though its incidence appears to differ between the underlying disease, varying between 2-14% for aneurysmal disease²⁵⁻²⁸ and between 4.6-7% for occlusive disease^{29,30}. **Chapter 5** evaluated the incidence and nature of SSI following open aortoiliac surgery for aneurysmal vs occlusive arterial disease by comparing two retrospective cohorts of patients. Comparing 301 aneurysmal patients with 213 occlusive patients, 32 (5.9%) developed an SSI. Ten (3.3%) in aneurysmal disease vs.

22 (10.3%) in occlusive disease ($P = 0.001$). Likewise, infection-related readmissions and infection-related re-intervention were more frequent in occlusive disease. Logistic regression showed occlusive disease (OR 3.27, 95% confidence interval 1.38-7.78, $P = 0.007$) and chronic renal disease (OR 6.60, 95%CI 1.17-37.43, $P = 0.033$) to be determinants for SSI. An interesting distribution was found in the distribution of infectious pathogens, with 64% of SSIs in occlusive disease being caused by *S. aureus*, compared to 10% of SSIs after aneurysmal disease. Though no literature was recovered on the difference in SSI incidence after occlusive or aneurysmal disease, we theorize that this discrepancy can be attributed to two factors. One factor being that common risk factors for occlusive disease such as age, diabetes mellitus, smoking and dyslipidaemia are all associated with decreased tissue perfusion³¹⁻³⁴. Besides this, occlusive disease itself is associated with microcirculatory dysfunction³⁵⁻³⁷. Proper microcirculation being a prerequisite for appropriate wound healing, we assume the stenotic nature of occlusive disease is an underlying cause of the higher SSI rate. Another factor in the higher SSI rate in occlusive arterial disease is the use of inguinal incisions, a known risk factor for SSI development²⁵. Our analysis showed strong collinearity between occlusive arterial disease and the use of inguinal surgical access, meaning the risk of inguinal incisions may be inherent to the surgical treatment of occlusive arterial disease. Due to the higher incidence in SSI in occlusive disease, this patient group should be closely monitored to prevent further morbidity and mortality from SSIs.

Though SSIs are more common after occlusive surgery, they still represent a major cause for morbidity in aortic aneurysm surgery. The incidence of SSI is reported to be between 0.5% and 1.5% for endovascular aneurysm surgery and between 2% and 14% for open aneurysm surgery^{24,26-28}. As aortic aneurysm surgery utilizes prosthetic grafts, it carries a high risk of prosthetic graft infection, which in turn is associated with amputation rates up to 11% and mortality varying between 20%-40%³⁸⁻⁴⁰. **Chapter 6** assessed the incidence and outcome of SSI and graft infection in open and endovascular abdominal aortic aneurysm surgery. A retrospective cohort of 636 elective aneurysm patients developed to 20 (2.7%) SSIs, of which eleven (2.7%) were after endovascular and 9 (4.0%) were after open surgery ($P = 0.352$). In a mean follow-up duration of 49 months 24 (2.8%) graft infections occurred. Eight (1.7%) graft infections developed following endovascular repair vs sixteen (4.3%, $P = 0.023$) after open repair, with 83.3% requiring infection-related surgery. Logistic regression revealed that SSI was a risk factor for graft infection (OR 7.1 95% CI 2.1-24.0, $P < 0.0001$). The incidence of graft infection parallels the 0.6%-3.0% incidence in literature⁴¹⁻⁴³. It might be worth investigating whether routine long-term antibiotic prophylaxis in patients with a SSI after aortic graft surgery reduces the risk of aortic graft infection. Another, less invasive option would be to subject patients who develop a SSI after aortic graft implantation to intensified follow-up with more frequent radiographic imaging. We suggest that this follow-up period should constitute at least the first year after surgery, seeing as 70% of graft infections occurred within one year after surgery. Since most SSIs and graft infections in aortic

aneurysmal surgery were caused by *S. aureus*, preventing *S. aureus* SSI as mentioned in **Chapters 2 and 3** could prevent the development of graft infections.

FUTURE PERSPECTIVES

As the prevalence of vascular disease rises with age, an increase in vascular procedures is expected to accompany the aging population ⁴⁴. Age being an independent risk factor for SSI ⁴⁵, a rise in the incidence and prevalence of SSI in vascular surgery must be anticipated. To combat a surge of infections in a world with rapidly growing bacterial resistance to antibiotic medication, new therapies and preventative measures will have to be implemented, while maintaining the current standards of perioperative infection prevention.

Bacterial antibiotic resistance is increasing to alarming levels globally. Also, the use of mupirocin treatment to eradicate *S. aureus* has led to mupirocin resistance and treatment failures. While short-term use of nasal mupirocin for perioperative prophylaxis has not been associated with an increase in mupirocin resistance ^{46–49}, when used over long periods of time, resistance has been shown to reach high levels ^{50,51}. A first implementation in practice should be to treat only those patients who benefit from eradication treatment. As Chapter 2 and 3 have shown, patients undergoing peripheral bypass surgery had no reduction in the number of SSIs and should not be pre-operatively treated. It is important to repeat that screening is an important part of eradication therapy since this greatly reduces antibiotic therapy in lieu of slightly increased costs. Since patients undergoing emergency procedures have elevated infection risk without the time to wait for screening, this group should be treated without screening.

Since eradication treatment reduces the risk of SSI, other treatment methods should be considered for future use ⁵². Pre-operative showering with antiseptic soap has proven inferior to mupirocin and chlorhexidine-based eradication therapy ⁵³. Recent research on the use of retapamulin for the eradication of mupirocin resistant *S. aureus* showed a reduction in nasal MRSA 1 week following therapy, though results were not sustained after 6 weeks ⁵⁴. Despite this, it might be a viable alternative to mupirocin in the perioperative eradication of resistant *S. aureus*. Another alternative in nasal eradication therapy is povidone-iodine (PI). A prospective trial comparing preoperative mupirocin vs PI found deep SSI in 5 out of 776 patients treated with mupirocin and 0 out of 763 patients treated with PI. However, the study patients were not followed after discharge, and a comparison in postoperative nasal cultures showed 92% negative cultures after mupirocin vs 54% negative cultures after PI ($P = 0.03$) ⁵⁵. Another study retrospectively comparing intranasal PI vs no therapy reported a lower SSI rate after PI (1.1% vs 3.8% $P = 0.02$) ⁵⁶. A trial testing the effectiveness of nasal application of 70% ethanol in the eradication of *S. aureus*-colonized of health care workers described a reduction in *S. aureus* between 82% and 99% ⁵⁷. Though this seems promising, no trials using alcohol-based nasal antiseptic have been performed in patients undergoing surgery, so its effects on SSI reduction are unknown.

Another proposed method in the prevention of SSI is negative pressure wound therapy (NPWT). NPWT utilizes intermittent or continuous sub-atmospheric pressure on a wound by means of a pump and wound dressing. It has become a common modality in the treatment of chronic wounds and skin grafts ^{58–60} and suggested mechanisms of action include increasing blood circulation by angiogenesis, removing oedema and dead space, increasing granulation tissue formation, and decreasing bacterial load ^{61–63}. Recent research has focussed on the application of NPWT on closed surgical incisions to prevent SSI. A recent review of the literature reported a potential reduction in SSI with prophylactic NPWT, though most studies included lacked control groups. The largest randomised controlled trial included showed a decrease in infection rate from 18.9% with sterile dry dressings to 9.9% with NPWT ($P = 0.049$) ^{64,65}. One study reported the use of prophylactic NPWT in vascular surgery ⁶⁶. It prospectively followed 52 patients with NPWT after a groin incision and compared them to a retrospectively reviewed cohort of 63. NPWT reduced the incidence of infection from 30% to 6% ($P = 0.001$) and reduced deep infections from 3% to 0. Since most evidence for the prophylactic use of NPWT in the prevention of SSI is low-quality, large trials for its efficacy and cost-effectiveness are encouraged.

CONCLUSION

In this thesis, the prevention, outcome and risk factors of SSI were evaluated, along with prognostic factors for optimizing EVAR follow-up. SSI is a major complication after vascular surgery and causes high morbidity and health costs, and potentially leads to graft infection and death. It is associated with occlusive vascular disease and groin incisions and is as common in endovascular AAA treatment as in open AAA surgery. Perioperative eradication therapy is a cost-effective method to prevent *S. aureus* SSI in aortoiliac surgery.

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Chapter 8

Impact Paragraph

The goal of this thesis was to describe the factors that influence post-operative complications after vascular surgery and to offer solutions where possible. Surgical site infection (SSI) is a major complication after vascular surgery and causes high morbidity and health costs. On the subject of preventing SSIs, this thesis offers various risk factors to guide clinicians and surgeons, as well as preventative measures to counter possible morbidity and mortality. This thesis presents various insights in vascular surgery and infection management that contribute to optimizing care for vascular surgery patients.

As described in the general discussion in this thesis, a huge worldwide problem is growing bacterial resistance to antimicrobial therapies. This thesis presents ideas to prevent SSIs in vascular surgery without contributing to the ever-growing antibiotic resistance. The eradication of *S. aureus* prior to certain vascular procedures reduces post-operative infections with a minimal risk to increasing bacterial resistance. Furthermore, the general discussion describes promising emerging methods of *S. aureus* eradication therapy that might be effective even in antibiotic resistant bacteria. The findings in this thesis have led to a change in perioperative care in the Amphia Hospital, Breda. Screening and eradication of *S. aureus* has become standard care prior to vascular surgery in groups that benefit from eradication therapy. To avoid contributing to bacterial resistance to mupirocin, the Amphia Hospital has reserved their screening and eradication regimen for patient groups that have been proven to benefit from it instead of treating every vascular patient with preventive antibiotic treatment.

Since antibiotic therapies seem to have a finite usability in the light of growing bacterial resistance, we tried to elaborate on our experimental research by searching for possible future methods of *S. aureus* eradication treatment.

Our research shows that SSIs can be just as common after endovascular surgery as after open vascular surgery. This finding should caution vascular surgeons to remain alert even after, usually deemed safer, endovascular therapy. We also found a strong correlation between SSI and the potential life-threatening infection of vascular grafts. Because of this finding, we postulated two questions for further research on this subject. Does long-term antibiotic use prevent graft infection after surgical site infection? Or could graft infection be diagnosed early by subjecting patients who developed SSI to frequent radiographic imaging?

Concerning patient safety and patient-friendly surgery, we analysed the infection risk between performing one or two operations in patients with arterial occlusive disease. It showed that a hybrid procedure combining open femoral endarterectomy with endovascular revascularization is a safe procedure without significant differences in infection rates. Also, hybrid revascularization is more cost-effective than two separate procedures and more patient-friendly due to the comfort of only having to undergo one surgical session, combined with shorter hospital stay.

The results of this thesis have been made public through publication in international scientific journals and by means of presentation on international symposia. Through discussion with doctors and scientists from over the world we have sought to add to the general knowledge on vascular surgery complications and reduce the risk of SSIs and graft infections with their associated morbidity and mortality for patients around the world.

Chapter 9

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List of publications

Curriculum Vitae

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Anniek en Jonathan, als ex-roomies van Roos hebben jullie me zodra de goede envelop open mocht direct hartelijk ontvangen en de vriendschap bezegeld met een brownie-wedstrijd. Jullie staan altijd klaar voor ons als er hulp nodig is, of het nou gaat om klussen, verhuizen, een huwelijk verzorgen, een koelkast leegdrinken of gewoon goed advies geven. Super om jullie tot mijn vrienden te mogen rekenen.

Jiroh, waar te beginnen. Toen ik bij Robbert opperde om jou te vragen als nieuwe gitarist voor de band had niemand dit aan zien komen. Als onnavolgbaar en ongeleid projectiel weet je zeker dat elke situatie waar je met Jiroh inkomt totaal anders gaat zijn dan je had kunnen bedenken. Afgelopen jaar was wat saai voor ons omdat we nergens muziek mochten maken, maar zodra dat weer kan kijk ik uit naar de bizarre avonturen en optredens die we samen gaan maken.

Dennis, van ‘gezellig gevormde’ bandgenoten (laten we het op afgerond 100kg houden) tot klim- en bergsportpartners. Van de Guinness en shoarma elk weekend tot de 14 uur durende klimtochten waarbij we niet zeker waren of we heelhuids weer terug zouden komen. Wie had gedacht dat die ene keer mee gaan klimmen in Roosendaal ons leven zo enorm zou vormen. Zonder die broodnodige ontspanning had ik nooit de energie gehad om mijn werk, laat staan het onderzoek ernaast, vol te houden. Gelukkig heb ik als dit boekje af is veel meer tijd om buiten op avontuur te gaan als dat weer mag. Nu vrouw en kinderen nog zo ver zien te krijgen...

Robbert en Marijke, lieve broer en zus, of het nou ontspanning was in de vorm van goede muziek en nog beter bier, of de vriendschappelijke competitie wie er als eerste zijn promotie klaar zou hebben, zonder jullie had ik dit nooit op deze manier klaar kunnen krijgen. Door jullie voorbeeld heb ik ook ingezien hoe belangrijk je eigen leven naast het werk is, iets wat nog veel duidelijker is nu ik een eigen jong gezin heb. Marijke, gelukkig heb ik iets terug kunnen doen door je advies te geven toen je in dezelfde twijfel als ik verkeerde over je toekomst. Ik ben ervan overtuigd dat we allebei een goede keuze gemaakt hebben.

Lieve **pa en ma**, jullie hebben me altijd gesteund, in alles wat ik deed. Met af en toe een beetje bijsturing als ik voor de 4^e week op rij iets te beschonken thuiskwam. Ik kan niet meer bijhouden hoe vaak jullie midden in de nacht stad en land doorkruisten omdat je zoons zo nodig ergens op moesten treden. Niets was te gek en we hebben allemaal de ruimte en steun gekregen om ons te ontwikkelen tot wie we wilden zijn.

De goedbedoelde vraag: ‘Hoe staat het nu met je proefschrift?’ als ik bij jullie een weekendje kwam ontsnappen aan werk en onderzoek werd door mij niet altijd even enthousiast beantwoord. Maar daardoor had ik de week erop net wat extra motivatie. Dankjewel daarvoor! Niemand kan zich fijnere ouders en een beter voorbeeld voor de toekomst wensen. Ik hoop dat wij onze kinderen half zo goed bij kunnen staan als jullie voor mij hebben gedaan en nog altijd doen!

Kodi, ongelooflijk wat zo’n klein beest met je kan doen als mens. Het huis was een stuk gezelliger om artikelen te zitten typen en de verplichte wandelingen waren altijd een goede oppepper om daarna weer aan de slag te gaan. Het werkt niet altijd even makkelijk met een 23kg zware bonk liefde op schoot, maar het wordt er zeker gezelliger op.

Roosmarijn, lief, wat fijn dat je in mijn leven gekomen bent. Ik was er zo van overtuigd dat ik Breda zou verlaten en alles uit Breda daar zou laten om in Rotterdam verder te gaan. En dan zit je een maand later in een vliegtuig naar Bologna om samen het nieuwe jaar te vieren. Alles is zo makkelijk met jou dat het bijna vanzelf gaat. Een hond met allebei een drukke baan, geen probleem. In 3 dagen een huis kopen, zo gepiept. Trouwen in coronatijd, moet gewoon kunnen. En nu sinds een paar maanden ons prachtige zoontje er is, wordt het leven er alleen maar mooier op. Nu dit proefschrift klaar is krijgen we samen nog meer tijd voor

ons prachtige gezin. Wat de toekomst ook gaat brengen, met jou naast me kan ik het zeker aan.

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CURRICULUM VITAE

Jasper Langenberg was born on March 31st, 1989 in Halsteren, the Netherlands. He attended secondary school at Roncalli in Bergen op Zoom. He started his medical studies at Leiden University in 2008.

After graduation in 2014 he started as a surgical resident in the Amphia Hospital in Breda. In the following year, he started his PhD project in vascular surgery under supervision of dr. L. van der Laan alongside his residency. In 2017 he interrupted his residency to manage a study on the effects of prehabilitation in the elder surgical population. He transferred to the Ikazia Hospital in Rotterdam in

February 2018 to continue his work as resident doctor and started the general residency program in 2019 under supervision of dr. P.T. den Hoed. In 2020 he decided to quit to pursue a different career path. He is currently working at the Intensive Care Unit during the Coronavirus pandemic.

In his free time, he is an avid rock climber and runner. He is a passionate accordion player in Irish folk music with two recorded albums and shows in both the Netherlands and abroad.

He lives with his wife Roosmarijn and son Daniël in Heinenoord.