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Topical Gentamicin and Vancomycin for Surgical Site Infection Prophylaxis in Patients 5. Undergoing High-Risk Vascular Surgery

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Abstract

Introduction: Arterial surgery using a groin incision has a high incidence of surgical site infection (SSI), which is morbid and costly. Gentamicin-eluting collagen sponges and vancomycin powder are effective SSI prophylaxis for nonvascular operations. Feasibility of a prospective trial of SSI incidence after high-risk arterial surgery with topical gentamicin and vancomycin was assessed.

Methods: A randomized controlled feasibility trial enrolling 32 patients with ≥1 of obesity, diabetes, reoperation, tissue loss or dialysis. In 41 groin incisions, 21 had standard closure and 20 had closure with topical gentamicin and vancomycin. Primary feasibility outcomes and secondary clinical outcomes were recorded at 90 days.

Results: Feasibility was achieved in all metrics. SSI was reported in 13 patients (31.7%), 8 (38.1%) standard and 5 (25.0%) experimental patients.

Conclusion: Gentamicin-eluting collagen sponge and vancomycin powder use in high-risk groin incisions is feasible for study. There was a trend towards fewer infections in the experimental arm.

Keywords

Vascular surgery, surgical site infection, topical antibiotics, gentamicin-eluting collagen sponge, vancomycin powder

Summary for Lay Audience

Operations performed by vascular surgeons commonly involve groin incisions to expose the femoral arteries. Infection in these incisions, known as surgical site infections (SSI), are common and occur much more often than after other types of surgery. Certain patients, such as obese patients, diabetic patients, renal failure patients on dialysis, patients having a redo surgery or who have tissue loss from poor blood flow are at especially high-risk of developing SSI. SSI in a groin incision after a vascular operation is usually treated with antibiotics, as well as opening and packing the wound with a dressing until it heals from the bottom up. In some cases, SSI can require reoperation or even amputation of the surgical limb because of infection involving the recently operated blood vessel or associated graft (fabric tube sewn to a hole in the artery). SSI cause additional discomfort for the patient and are costly to the healthcare system. There are few strategies that are effective in preventing groin incision SSI after vascular surgery. Different surgeons, such as cardiac and orthopaedic surgeons, have shown antibiotics placed in the surgical incision prior to closure can prevent SSI. We are interested in assessing whether placing a gentamicin-eluting collagen sponge and vancomycin powder in the incision prior to closure prevents SSI in high-risk patients. We conducted a feasibility study to determine whether such a study could practically be performed.

We recruited 32 patients with 41 groin incisions who had at least one major risk factor for groin SSI. We randomly assigned 21 to the usual method of groin incision closure and 20 to the topical gentamicin and vancomycin group on a per-groin basis. We found the study to be feasible in all aspects. SSI developed in 31.7% or 13 of the 41 groin incisions. Eight of 21 patients in the standard closure group, or 38.1%, and 5 of 20 in the topical antibiotics group, or 25.0%, developed SSI. The difference between the groups was 13.1%. Using these results, we plan to carry out a full-scale study to assess if gentamicin-eluting collagen sponges combined with vancomycin powder prevent SSI.

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ABI – ankle-brachial index

BASIL – Bypass versus Angioplasty in Severe Ischemia of the Leg

BMC2 VIC – Blue Cross Blue Shield of Michigan Cardiovascular Consortium Vascular Intervention Collaborative

BMI – body mass index

CDC – Center for Disease

ED – emergency department

CI – confidence interval

GFR – glomerular filtration rate

IV – intravenous

LER – lower extremity revascularization

MIC – minimum inhibitory concentration

MRSA – methicillin-resistant *S. aureus*

NNIS – National Nosocomial Infection Surveillance program

NNT – number needed to treat

NPWT – negative pressure wound therapy

NR – not reported

NSQIP – National Surgical Quality Improvement Program

OR – odds ratio

PTFE – polytetrafluoroethylene

RCT – randomized controlled trial

RR – relative risk

SSI – surgical site infection

VQI – Vascular Quality Initiative

Chapter 1

1. Introduction

Lower extremity revascularization (LER) remains one of the mainstays of modern vascular surgery. Surgical site infection (SSI) represents a common source of morbidity for patients undergoing LER. The reported incidence of SSI in these patients is consistently higher than that for other "clean" surgical procedures as defined by the CDC[1,2]. Furthermore, SSI incurs significant healthcare-related costs and potentially catastrophic limb-related consequences. The pathogenesis of these infections is multifactorial and the etiologic organisms diverse[1].

Measures to prevent SSI in patients undergoing LER are described in the 1999 CDC guidelines including appropriate patient skin preparation, sterilization and antimicrobial prophylaxis[2]. Given the elevated rates of SSI in patients requiring LER, there exists substantial interest in the vascular surgery community with regards to additional measures that may reduce SSI and its associated morbidity. A variety of strategies have been subject to study however, the supporting evidence for individual techniques is sparse and little consensus exists as to whether such techniques are truly effective or in whom they should be implemented[3]. Topical antibiotics have emerged as a useful adjunct to reduce SSI in other surgical disciplines, notably cardiac and orthopaedic surgery[4,5].

Preliminary investigations in patients undergoing LER suggest benefits with topical antibiotic administration as well, yet these studies are small and suffer from potential methodological issues[6,7]. Combining different topical antibiotics to target both gram negative and gram-positive bacteria in patients undergoing LER for the prevention of groin SSI has yet to be explored.

1.1 Definition of SSI

SSI are infections involving a recent surgical site. The most widely used definition of SSI has been put forth by the CDC in 1992[8]. The CDC definition is used by the National Nosocomial Infection Surveillance (NNIS) program in the United States and supported by the American College of Surgeons as well as many other international, national, and

specialty societies, including Infection Prevention and Control Canada. Procedures are classified into 4 categories (clean, clean/contaminated, contaminated and dirty) based on clinical characteristics and this scheme is used to stratify SSI risk according to operation[2]. According to the 1992 CDC definition, a SSI infection encompasses incisional and organ/space SSI.

Incisional SSI are further divided into superficial SSI if involving only the skin and subcutaneous tissue versus deep incisional SSI if involving the deep fascial and muscle layers. Organ/space SSI involve any part of anatomy manipulated during the operation other than the incision itself. SSI are defined within 30-90 days of depending on the procedure, however this period extends to 1 year for deep incisional and organ/space SSI in the presence of a prosthetic implant[2]. 90-day monitoring is recommended for LER.

Criteria defining superficial SSI require at least one of: purulent incisional drainage, pathogen-positive culture, at least one cardinal sign of inflammation, or diagnosis of superficial SSI by the attending surgeon. Deep incisional SSI are defined by one of: purulent drainage from deep tissues, spontaneous wound dehiscence in the presence of fever or localized tenderness, abscess diagnosed surgically/radiographically/histopathologically, or diagnosis of deep SSI by the attending surgeon. Organ/space SSI are defined by purulent drainage from the organ/space, pathogen-positive culture from the organ/space, organ/space abscess identified surgically/radiographically/histopathologically, or diagnosis of organ/space SSI by the attending surgeon[2].

The vascular surgery literature to date has used several definitions and periods of monitoring for SSI. This inconsistency has had a substantial impact on the epidemiology of SSI after vascular surgery. Several vascular surgery-specific classification systems for SSI exist, of which, the Szilagyi classification system devised in 1972 based on a retrospective cohort of prosthetic graft infections is most widely used[9]. This definition, like the CDC definition, divides SSI into 3 grades based on depth of infection. Grade 1 SSI are confined to the epidermis/dermis, Grade 2 SSI involve deeper subcutaneous

tissues and Grade 3 infections involve the arterial implant. Importantly, no specific criteria defining each Szilagyi Grade are provided, permitting some subjectivity in the diagnosis of vascular SSI. Alternative classification systems for vascular SSI are based on extent of graft involvement or time since the index operation. Large registries of vascular procedural outcomes further adopt SSI definitions limited by the available dataset. For example, the Vascular Quality Initiative (VQI), a large North American registry of vascular operative outcomes, defines SSI based only on the presence of a positive wound culture or antibiotic administration during the index hospitalization[10].

The significance of these different definitions of SSI is reflected in the highly variable epidemiology and outcomes of vascular SSI in the literature as will be discussed next.

1.2 Epidemiology of SSI Complicating LER

The incidence of SSI after LER varies widely in the reported literature depending on the design and follow-up period of the study, and the risk profile of the included patients. Large retrospective registry data, meta-analyses of institutional cohorts and a select few randomized controlled studies inform the current understanding of the incidence of SSI following LER, estimated at 4-40% across a range of studies as described below. These figures are in excess of the CDC average for other clean procedures at 5%[2].

Few methodologically sound randomized controlled trials exist in the published literature regarding outcomes of lower extremity revascularization. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial is the most widely cited study in this regard[11]. BASIL, conducted in 27 U.K hospitals with its initial results published in 2005, compared amputation-free survival in 452 patients randomized to infrainguinal bypass or balloon angioplasty for severe peripheral arterial disease. The surgical arm, comprising 228 bypasses, had SSI complicate 22.8% of procedures within 30 days, accounting for a substantial portion of the higher morbidity of surgery (57 vs. 41%, 95% CI 5.8-24.5) and the increased costs[11].

Several multi-institutional registries have been created to accurately track outcomes following many different vascular operations. Prominent among these, are the VQI mentioned earlier, as well as the more broadly aimed American College of Surgeons-National Surgical Quality Improvement Program. Recent reviews of these registries have noted SSI rates of 4.8-11.1% complicating LER. The VQI registry, supported by The Society of Vascular Surgery, is maintained by voluntary submission of data concerning a wide range of vascular operations by hundreds of surgeons at multiple academic and community hospitals. In a 2014 review of 7908 lower extremity bypass procedures submitted to the VQI, SSI data were tracked during the index hospitalization only, revealing an in-hospital SSI rate of 4.8%[10]. The primary limitation of the VQI registry is the short monitoring period, after which many vascular SSI present. The NSQIP registry tracks outcomes for 30-days using 30-day interviews and chart reviews conducted by trained personnel. Review of 12 330 registry infrainguinal revascularizations published in 2015 revealed a SSI incidence of 11.1%[12]. This is likely more reflective of SSI incidence in this population than the VQI data given the longer follow-up period. In 2017 a 35-hospital Michigan-based vascular surgery registry, The Blue Cross Blue Shield of Michigan Cardiovascular Consortium Vascular Intervention Collaborative (BMC2 VIC), reported a SSI rate of 10.1% among 3033 patients undergoing a variety of extra-anatomic aortoiliac and infrainguinal bypass operations[13].

Single-institution retrospective reviews are subject to multiple forms of bias including publication bias and varying patient selection, resulting in variable outcomes. Meta-analyses of these studies have been conducted to provide more generalizable results. A 2015 meta-analysis of retrospective studies assessing the performance of femoral-popliteal bypass calculated a combined SSI rate of 7.8% in 38 articles with 6374 bypasses. Including graft infections however, the overall infectious complication rate was 10.2%[14].

None of the these widely cited studies analyzed SSI incidence out to 90 days, as recommended by the CDC. A recent review of the NSQIP database revealed that SSI after major vascular surgery most frequently occurs post-discharge[15]. A 2019 single-institution cohort of 256 patients undergoing vascular operations through groin incisions documented a 180-day wound complication rate of 23%, with half of these presenting

after 30 days with a major (as opposed to minor) wound complication. Most wound complications were infectious in nature necessitating the use of antibiotics[16].

The incidence of SSI after lower extremity revascularization likely approximates 10-20% at the 90-day checkpoint as recommended by the CDC. Important conclusions from the literature described above include the poor reporting of accurate definitions and incidence data concerning SSI after LER, as well as the established propensity of these events to occur beyond the typical 30-day monitoring window for SSI. Regardless, SSI complicates a clinically meaningful number of reconstructions, with important implications to patient outcomes as discussed next.

1.3 Morbidity of SSI

Vascular SSI involving a groin incision may result in substantial morbidity to the patient. Many studies have documented increased morbidity and healthcare costs associated with vascular SSI. The NSQIP database documented higher rates of graft failure (OR 2.3, 95% CI 1.7-3.1), reoperation (OR 3.7, 95% CI 3.1-4.6) and prolonged length of stay (OR 1.8, 95% CI 1.4-2.1) in their 1367 patients with vascular SSI following LER compared to 10 963 without SSI. No association with mortality was noted[12]. Among 320 patients with SSI after LER compared to 2713 patients without SSI, the BMC2 VIC registry similarly found higher rates of reoperation (3.9% vs 0.4%, $p<0.01$) and readmission (4.8% vs. 1.0%, $p<0.01$), as well as major amputation (9.0% vs. 2.3%, $p<0.01$). Again, no association with mortality was found[13]. These large-scale studies demonstrate that SSI can not only produce infection-related morbidity but threaten the integrity of the vascular reconstruction itself.

It has been appreciated over time that serious morbidity related to vascular SSI often occurs after hospital discharge, and particularly outside the typical 30-day monitoring period for complications after surgery. For example, Wiseman *et al.* specifically studied vascular SSI following hospital discharge in the NSQIP database and found that these patients underwent reoperation at impressively higher rates than those without post-discharge SSI (39% vs. 12%, $p<001$)[15]. In a recent single institution review, Audu *et al.* noted that the 30-day incidence of major SSI-related morbidity (readmission or

reoperation) was only 3% at 30 days but rose to approximately 13% by the 90-day interval thereafter remaining stable to 180 days[16]. These studies reinforce the morbidity of SSI and highlight the importance of prolonged monitoring LER incisions.

Infection of a vascular prosthesis remains one of the most feared complications following LER, associated with high mortality and limb loss rates in the setting of aortic and lower extremity graft infection respectively[17]. Several mechanisms of graft contamination are described, including direct extension of a SSI to involve the prosthesis[1]. A large case-control study from the Mayo clinic identified groin incisions and wound infection as major risk factors for lower extremity arterial prosthetic graft infection (OR 4.1, 95% CI 1.6-10.7, p=0.003 and OR 5.1, 95% CI 1.6-16.2, p=0.005). Early (<6 months) graft infection represented nearly half of the cases with half of the early graft infections associated with a wound infection[17]. Other studies have similarly noted the relationship between vascular graft infection and SSI[18]. Evidently, SSI in the groin places a vascular reconstruction at risk of infection with potentially catastrophic consequences.

1.4 Pathogenesis and Microbiology of SSI

SSI is a result of microbial contamination of a surgical wound. The risk of infection at a given site is related to the virulence of the organism, the dose of pathogen and the resistance of the host. It has been shown experimentally that a contaminating dose 10^5 microorganisms/gram of tissue dramatically increases the risk of SSI and this threshold is reduced roughly 1000-fold in the presence of foreign material[19-21]. Many vascular operations involve the implantation of a prosthetic vascular graft composed of either polyester or polytetrafluoroethylene (PTFE). The implantation of such grafts places these wounds at high-risk for colonization and infection.

The majority of SSI are a consequence of wound contamination by endogenous patient flora, the specific pathogen dependent largely on the surgical site[1]. Introduction of pathogens by the surgical team via breaks in sterile technique are also relevant as are contaminated wounds and pre-existing remote infections. Vascular SSI are most frequently caused by gram-positive organisms, particularly *Staphylococcus aureus*

accounting for up to 80%[1,9,22,23]. *Staphylococcus epidermidis* is also prevalent, with this species' ability to produce biofilms rendering them particularly challenging to eradicate[1]. Incisions involving the groin are prone to gram-negative and anaerobic organism contamination due to fecal spread[1,2]. Indeed 20-25% of SSI after LER are a result of gram-negative bacteria[1]. Polymicrobial infection is documented in about 25% of cases[1]. MRSA, oxacillin-resistant *S. epidermidis*, *Pseudomonas aeruginosa* and other organisms harboring antimicrobial resistance have assumed increasing prevalence over recent years[1,24]. Some studies have identified increased morbidity due to SSI caused by resistant organisms[24].

1.5 Risk Factors for SSI

Given the high incidence and significant morbidity associated with SSI after LER, substantial effort has been made to identify those patients at highest risk of developing SSI after LER, in order to provide optimal prophylaxis and monitoring of these patients. The CDC Guideline for SSI Prevention defines patient, preoperative, intraoperative and postoperative risk factors for SSI among a broad range of surgical patients supported by mostly retrospective evidence. Diabetes mellitus and obesity are among the described patient-related risk factors of importance[2].

1.5.1 Groin Incision

Vascular operations undertaken through a groin incision are thought to be at highest risk for SSI [1,9,15,25]. Furthermore. lower extremity bypass procedures have the highest reported SSI rates among vascular operations[9]. Identifying patients requiring a groin incision preoperatively allows for stratification of SSI risk.

1.5.2 Patient, Procedure and Hospital Risk Factors

Recent large registry studies have sought to define risk factors associated with SSI complicating LER. Among both the BMC2-VIC and NSQIP studies with 30-day follow-up, obesity (BMC2-VIC OR 1.78 95% CI 1.23-2.57, p=0.002, NSQIP OR 2.1 95% CI 1.8-2.4) and dialysis dependence (BMC2-VIC OR 4.35 95% CI 3.45-5.47, p<0.001, NSQIP OR 1.51 95% CI 1.0.8-2.11) were significantly associated with vascular SSI

among other variables[12,13]. The BMC2-VIC study identified prior PCI, severe symptoms, congestive heart failure, hypertension, antiplatelet use and chronic kidney disease as other predictive patient-related factors. Significant procedure-related variables included concomitant stent placement, intraoperative graft thrombosis, iodine-only skin preparation and intraoperative serum glucose >180mg/dL. Hospital related predictors were teaching hospital and low volume setting[12]. In the NSQIP registry female sex, chronic obstructive pulmonary disease, preoperative hyponatremia and surgery >4 hours were additional factors predictive of vascular SSI[13].

The VQI registry in contrast, with its lower overall SSI incidence and shorter follow-up period found procedural variables such as duration of surgery >220 minutes, transfusion >2 units packed red blood cells and skin preparation without chlorhexidine-based products were significantly associated with SSI on multivariate analysis. Pre-operative ABI <0.35 was the only predictive patient-related factor[10].

The more recent NSQIP review specifically addressing post-discharge SSI after major vascular surgery highlighted obesity, diabetes mellitus, critical limb ischemia (including tissue loss) and other comorbidities as predictive of post-discharge SSI. This was in contrast to in-hospital SSI, which was largely predicted by multiple perioperative variables. As mentioned above, the SSI rate was much higher after discharge than during the index hospitalization and post-discharge SSI was significantly associated with more major morbidity. The authors devised a four-tier risk-prediction model for SSI after major vascular surgery based on multiple factors with excellent agreement between their observed and predicted data. This model requires clinical validation however, its demonstrated feasibility supports the notion of stratifying patient SSI risk prior to vascular surgery[15]. Retrospective single-institution studies lend further support to many of these variables as being predictive of SSI including obesity, diabetes mellitus, tissue loss and others[26,27,28].

The above data suggest that patients at high-risk for SSI complicating LER, in particular SSI associated with major morbidity, can be identified preoperatively based on the

severity of their ischemic disease, comorbidity profile and other demographic variables. Important risk factors include obesity, dialysis dependence, redo surgery, diabetes mellitus and critical limb ischemia associated with tissue loss or open wounds among others.

1.6 SSI Prophylaxis

Interest in measures to prevent SSI after LER have been rising as the substantial morbidity and cost of SSI have been borne out in the literature. In general, SSI prevention at most major hospitals follows the guidelines of the CDC[2]. In 1999 the CDC published a comprehensive document outlining the epidemiology, natural history and recommended preventative measures for SSI across all surgical disciplines. This document remains in use today, with published updates in recent years as further evidence has emerged pertaining to interventions for SSI prevention. Steps to prevent SSI in this guideline include appropriate antimicrobial prophylaxis, control of remote infections, minimizing perioperative transfusion and preoperative length of stay, antiseptic showers, appropriate patient and surgical team sterilization, control of the operating room environment and incision care. These recommendations have become incorporated as standard practice in most major hospitals[2].

Preventative measures for SSI after vascular surgery involving groin incisions have been recently reviewed[3]. Existing evidence supports the use of preoperative antiseptic shower, <24hr perioperative antibiotic prophylaxis, oblique (as opposed to longitudinal) groin incision, negative pressure wound therapy (NPWT) and gentamicin-eluting collagen sponge implants, as will be discussed further below. Nasal MRSA screening and decontamination was not recommended based on limited effectiveness.

1.6.1 Antiseptic Shower

Preoperative antiseptic shower was specifically studied in vascular surgery patients by *Earnshaw et al*. without demonstration of SSI reduction compared to other cleansing products[29]. This finding has been reported more broadly and in systematic

reviews, however the included studies suffer from methodologic issues including lack of compliance monitoring and the inclusion of varying wound classes in the dataset.

A retrospective study of chlorhexidine shower combined with oblique groin incision as a bundled intervention for LER and showed significant SSI reduction[30]. Laboratory evidence indicates chlorhexidine gluconate more effectively decontaminates the skin compared to iodine-based products, with a 9-fold reduction in skin bacterial counts compared to 2-fold with iodine[31]. Preoperative antiseptic shower the night before surgery is recommended by the CDC[2].

1.6.2 Perioperative Antibiotics

Perioperative antibiotic coverage for vascular surgery involving a vascular implant per the CDC includes <24hr of gram-positive coverage, typically cefazolin, given the predominance of skin-associated pathogens responsible for vascular SSI[2]. A 2007 meta-analysis of 10 randomized controlled trials of antibiotic prophylaxis in patients undergoing LER revealed significant SSI reduction in patients receiving prophylaxis compared to those without (RR 0.25, 95% CI 0.17-0.38, $p<0.00001$), although no individual study demonstrated significance independently. No differences in SSI incidence were noted with different duration of antibiotic prophylaxis, type of antibiotic and different dose regimens[32]. These data support current CDC recommendations for <24hr systemic gram-positive coverage during the perioperative period of LER.

Given the rising incidence and morbidity of beta-lactam resistant SSI, additional gram-positive coverage has been studied. Data from *Stone et al.* suggest incremental SSI reduction after vascular surgery by adding daptomycin or vancomycin to cefazolin compared to cefazolin coverage alone[33]. This finding requires further substantiation in future studies.

1.6.3 Type of Groin Incision

The groin is a high-risk surgical site for infection as described above. Reasons suggested for this include the proximity to the perineum, large burden of lymphatic tissue, and

bacterial overgrowth in the groin crease[1]. Groin incisions made obliquely from lateral to medial as one progresses proximal to distal on the thigh are thought to minimize lymphatic disruption. Multiple retrospective single institution reports, and meta-analysis of these studies, suggest decreased SSI, seroma, hematoma, lymphocele and overall wound complication incidence using oblique versus longitudinal incision[34-36]. A small single randomized controlled trial of 198 groin incisions failed to identify a significant impact of incision type[37]. Further study is required to resolve this conflicting evidence.

1.6.4 Negative Pressure Wound Therapy

NPWT has recently been investigated for its potential merits in preventing SSI following vascular surgery. Its use remains controversial due to high costs and conflicting evidence pertaining to its effectiveness at SSI prevention in specific groups of patients. Several randomized trials have been carried out to assess the ability of the device to prevent SSI in groin incisions. A recent meta-analysis of 935 patients undergoing vascular surgery via groin incision across 7 randomized controlled trials (4 in favor of NPWT) suggested substantial methodological issues with the existing studies. Meta-analysis was possible for 422 patients from 3 studies demonstrating significant SSI prevention with use of NPWT (RR 0.47, 95% CI 0.31-0.70)[38]. Similar findings have been reported in other recent meta-analyses involving vascular groin incisions[39]. Whether this potential benefit translates into cost-effectiveness remains to be defined. Currently NPWT is utilized as a preventative measure in a minority of vascular operations as it is expensive and logistically challenging to implement in the postoperative period.

1.7 Topical Antibiotics for SSI Prevention

The use of topical antibiotics for SSI prevention has been extensively investigated across multiple surgical disciplines in the past. While not routinely employed in most procedures, recent evidence has identified certain patient populations that stand to benefit from this therapy. Topical antibiotics have been experimentally shown to produce higher local concentrations of antibiotic compared to systemic administration with minimal systemic absorption. The primary concern regarding such an approach has been the selection of antibiotic-resistant organisms. No study, however, has demonstrated such a

finding. A contemporary Cochrane review of topical antibiotic use in surgery confirmed the benefits of topical antibiotic use on incisions healing by primary intention compared to no topical antibiotic among 8 randomized studies including 5427 patients (RR 0.61, 95% CI 0.42-0.87) with a NNT of 50[40]. Multiple regimens were described in the various included reports. Below the relevant literature pertaining to topical vancomycin and gentamicin for SSI prophylaxis are highlighted.

1.7.1 Vancomycin

Vancomycin is a bactericidal glycopeptide antibiotic excreted mainly by the kidney. It has a predominantly gram-positive spectrum of antibacterial activity, and its most widespread use is in the treatment of beta-lactam resistant infection, particularly MRSA. Major adverse events described with systemic vancomycin use include nephrotoxicity, ototoxicity, anaphylaxis and various dermatological complications including the red man syndrome[41].

Topical vancomycin in powder or paste form has been used for decades to prevent SSI in patients undergoing cardiac surgery. In a single institution randomized controlled trial of 416 patients, topical vancomycin was applied to the cut edges of sternotomies wounds of the interventional group and SSI incidence at 30 days was compared to patients without topical vancomycin. All patients received systemic antibiotic prophylaxis. SSI was significantly lower in patients receiving topical vancomycin versus controls (30-day SSI incidence 0.45% vs. 3.6% respectively, p=0.02)[42].

Further support for the use topical vancomycin as an adjunct comes from the orthopaedic literature. Several systematic reviews of the orthopaedic literature have been conducted, consisting predominantly of retrospective cohort studies or pre/post-intervention studies, showing significant SSI reduction with topical vancomycin use among spine, elbow, foot/ankle and total hip arthroplasty (OR 0.11-0.43 across the reviews)[5].

One observational study in vascular surgery patients undergoing open aorto-femoral or infrainguinal surgery at a single institution assessed the impact of topical vancomycin on

the incidence of groin SSI. Patients receiving topical vancomycin had the agent applied in a dose of 0.5g mixed in 500cc normal saline irrigation followed by 0.5g powder applied to the wound before closure. All patients received standard weight-based <24hr systemic antibiotic prophylaxis. SSI was noted in 25.1% of controls and 17.7% of topical vancomycin patients (p=0.049). The reduction in superficial SSI (18.9% vs. 11.5%, p=0.033) accounted for most of this benefit with no significant decrease in deep SSI incidence (6.1% vs. 5.7%, p=0.692)[43].

No adverse events have been specifically described pertaining to the use of topical vancomycin. Serum levels after topical vancomycin application have been occasionally reported as detectable, yet consistently at subtherapeutic concentration in studies using alternative agents for systemic prophylaxis. The potential for allergic reaction does exist, however[44,45].

1.6.2 Gentamicin

Gentamicin is a bactericidal aminoglycoside antibiotic agent excreted primarily by the kidney with a narrow therapeutic window. Its spectrum of activity includes gram-negative organisms and is effective against *Pseudomonas aeruginosa*. Potential serious toxicities at high serum levels include nephrotoxicity and ototoxicity. Anaphylaxis has also been reported[46].

Gentamicin as topical adjunct for SSI prevention is administered via a collagen-sponge carrier. The most widely used product is Collatamp G (EUSA Pharma Europe), which contains a fixed concentration of gentamicin throughout the sponge which comes in various sizes and can be cut to accommodate the size of the wound[47]. Pharmacokinetic studies have revealed initially high local concentrations of gentamicin, nearly 100-fold above the minimum-inhibitory concentration (MIC), which are maintained for 36hr after implantation. This is followed by rapid clearance of the antibiotic with minimal serum levels of gentamicin (1-4mg/L at 1-hour post-implant, 1.5mg/L after 24hr), well below the 10mg/L threshold for toxicity[48]. No adverse events specific to Collatamp G have been described, however there does exist a maximum dose limit of 9mg/kg bodyweight and its

merits in patients with renal failure, receiving concomitant nephrotoxic drugs or systemic gentamicin should be carefully considered[47].

Friberg reported the first large randomized controlled study evaluating the impact of Collatamp G in patients undergoing cardiovascular surgery. Collatamp G was used in 983 sternotomy closures and 967 patients served as controls. All patients received penicillin systemic antibiotic prophylaxis for 24-48 hours. SSI was detected in 9.0% of controls versus 4.3% of Collatamp G patients (RR 0.47, 95%CI 0.33-0.68, $p<0.001$). This was largely due to the reduced rate of superficial SSI (5.7% vs. 1.9%, 95% CI 0.20-0.57, $p<0.001$)[49]. The ability of gentamicin eluting sponges to prevent SSI in sternal wounds has been confirmed in a recent meta-analysis[4].

Few vascular surgery studies have addressed the use of gentamicin-eluting sponges for SSI prophylaxis[50]. A single randomized study of 40 patients undergoing prosthetic femoropopliteal bypass published in 2010 demonstrated no infections in the 30 patients randomized to a gentamicin-eluting sponge compared to 6 in the 30 patients receiving intravenous antibiotic prophylaxis only (0 vs. 20%, $p=0.024$). All SSI were deemed superficial and mean length of stay was longer in patients with SSI compared to those without (8.1 days vs. 5.7 days, $p=0.004$)[6]. Holdsworth *et al*. in 1999 reported a case series of 2 subsets of patients, those undergoing prophylactic gentamicin-eluting sponge placement for high SSI-risk vascular surgery and those receiving the adjunct for treatment of active infection at a vascular surgical site. None of the 12 prophylactic cases developed infection and 9/13 infections were cleared with no recurrence[51]. A prospective cohort study of hemodialysis access grafts documented no infections in a group of 20 patients receiving gentamicin-eluting sponge versus two infections among 20 contemporaneous controls[52]. Two other case series report favorable infection resolution rates with gentamicin-eluting sponge application to vascular surgical wounds[53,54]. Although limited by small sample sizes, these studies do suggest that gentamicin-eluting sponges can help prevent wound infections in vascular patients.

1.6.3 Combination Topical Antibiotic Prophylaxis

A single-center prospective study in cardiac surgery patients undergoing sternotomy published in 2017 evaluated a novel closing protocol consisting of vancomycin paste (3g in 4cc normal saline) applied to sternal wires and direct gentamicin application (160mg) to the sternal wires. Well-matched contemporary controls were compared to 932 patients after implementation of the novel protocol. SSI at 30 days was significantly reduced from 5.8% in controls to 2.0% in the combined local antibiotic group ($p<0.001$). The reduction was noted primarily in gram-positive infections. It is suspected that direct application of gentamicin to the wound, as opposed to via collagen-sponge or as a paste, resulted in rapid washout of the antibiotic and short duration of activity[55]. The findings of this study require validation, however, highlight the potential role for a broad-spectrum approach using a combination of local antibiotics to prevent SSI in high-risk wounds. Matching the antimicrobial spectrum of the agents used to expected pathogens at a given site is expected to produce clinically relevant reductions in SSI incidence, as has been observed using tailored systemic antibiotic prophylaxis[2].

1.8 Research Question and Hypothesis

This study will address the feasibility of a randomized controlled trial comparing the 90-day incidence of SSI following LER in high-risk groin incisions treated with topical vancomycin powder and a gentamicin-eluting sponge versus standard closure. Given that groin wound infections can be caused by both gram positive and gram-negative bacteria, we believe that a appropriately targeted topical antibiotic approach will prove effective in reducing the unacceptably high SSI rates in this patient population.

We propose to evaluate a prophylactic approach using the administration of topical vancomycin in combination with a gentamicin-eluding sponge to the groin wound of patients at high-risk for SSI based on the following risk factors for wound infection: an elevated BMI >30, tissue loss, redo surgery, diabetes mellitus or renal failure undergoing LER. We hypothesize that this combination of agents will be effective in reducing groin wound complications at 90 days when compared with usual care. We propose to conduct a feasibility study of our study protocol and procedures to help refine the protocol and guide sample size calculation for a future multicenter study.

Chapter 2

2. Study Design

This is a feasibility study for a single centre, double-blinded randomized, controlled trial to assess the impact of combined topical vancomycin and gentamicin-eluding sponge for SSI prophylaxis in patients undergoing vascular surgery who are at high risk of groin wound infections. Blinding includes outcome assessors and the study subjects.

A feasibility study was chosen prior to embarking on a full-scale randomized controlled trial for several reasons. First, there are limited studies evaluating similar protocols in this high-risk population for SSI, making estimation of an appropriate sample size challenging. Reported effect sizes for various topical antibiotics in different surgical settings are highly variable and were thought not to be accurate for purposes of our study. Our centre has no prior experience with gentamicin-eluting sponges in vascular cases and an assessment of the ease of use and the ability to obtain sponges to support our regular workflow was deemed prudent, which would inherently be assessed during the feasibility study. Finally, whether blinding of the subjects and outcome assessors could be maintained during the follow-up period, contributing substantially to the methodological quality of the study, was uncertain and thought best assessed by a feasibility study.

2.1 Patient Selection and Randomization

Inclusion Criteria:

Eligible patients, age >18 who have consented to undergo infrainguinal lower extremity revascularization with at least one of,

1. BMI >30
2. Tissue loss
3. Prior lower extremity surgery
4. Diabetes mellitus
5. Dialysis dependence

Such patients will be approached by one of the treating physicians (resident, consultant surgeon) and asked to be enrolled in the study using the informed consent sheet. Baseline demographic data will be collected by the investigators. Patients will be randomized per-

groin in the operating room using a central, third party, web-based computer program (www.sealedenvelop.com). Groin incisions will be allocated to either the interventional or control arm. Patients requiring bilateral groin incisions will have each groin randomized for enrolment in the study. Although we acknowledge that there is a loss of independence between patients when randomizing groins rather than patients, given that this was meant as a feasibility study we felt that the benefits in boosting the sample size would outweigh any statistical limitations with the loss of independence.

Exclusion Criteria:

Patients will be excluded if they meet any of the following criteria,

1. Patient refuses to participate
2. Patient has pre-existing cellulitis of the surgical groin
3. Patient has an allergy/known contraindication to cefazolin, gentamicin or vancomycin
4. Patient received antibiotics within 7 days prior to surgery
5. Patient is pregnant or breastfeeding due to teratogenicity of gentamicin
6. Patient is unable to communicate

2.2 Antibiotic Prophylaxis

Based on the results of randomization patients will receive 1) Standard perioperative antibiotic prophylaxis: cefazolin 1-2g IV (1g if <80kg, 2g if >80kg) 1 hr prior to induction of anaesthesia and q4h intraoperatively; if patients swab positive for MRSA pre-operatively, vancomycin 1g IV administered 1-2h prior to induction of anaesthesia as per standard practice will be given. 2) Standard perioperative prophylaxis plus 1g vancomycin mixed in 4mL normal saline and one 10x10cm Collatamp G sponge (containing 2.0mg/cm ^{2} gentamicin sulphate, total dose 200mg) cut to the size of the wound and applied intraoperatively to the superficial and subfascial compartments prior to closure. No placebo sponge was used in the control group due to the infectious risks of leaving a non-antibiotic impregnated foreign body in the wound.

2.3 Operative Conduct

At the time of surgery all patients will have hair removed from the surgical limb with clippers as necessary and prepared with chlorhexidene gluconate 2%w/v. All patients will

be draped in sterile fashion and the surgical team will scrub according to standard methods. Patient temperature will be maintained by the anaesthesia team with use of a bear-hugger. The patient will be randomized after induction of anesthesia by a surgical team member. The planned infrainguinal revascularization will then take place. For patients in the topical antibiotics group, immediately prior to closure of the incision, 1g of vancomycin will be mixed in 4mL of normal saline and applied as a paste directly to the fascia and subcutaneous tissue. The 10x10cm gentamicin-eluting collagen sponge will be cut to the appropriate size to cover the defect and applied after application of vancomycin. Closure will be performed with continuous 0 Vicryl suture for the fascia lata followed by 2-3 layers of continuous 2-0 Vicryl suture for the subcutaneous fatty and superficial fascial layers in which the topical antibiotics may reside. Staples or subcuticular 4-0 monofilament sutures will be used for skin closure. Following closure, the surgical site will be covered with 4x8cm gauze dressings folded in half to cover the incision, secured with dressing tape and left in place for 48hrs. For patients in the control group, the same closure protocol will be used without the use of topical antibiotics. The application of topical antibiotics and groin closure will be performed by a senior surgical team member without the other surgical team members (who will be assessing the wounds post-operatively for infection) present.

2.4 Surveillance

Patients will remain in hospital for 4-7 days post-operatively with regular monitoring by staff blinded to treatment allocation for signs and symptoms of SSI. Monitoring will include daily clinical exam for symptoms/signs of vancomycin or gentamicin toxicity (new-onset rash, tinnitus, hearing loss, renal failure etc) with serum vancomycin levels and gentamicin levels if suspicion of toxicity arises. Patients will receive regular home nursing wound care as required.

Patients will follow the regular post-operative surveillance schedule with the initial post-operative clinic visit at 4 weeks and 3 months post-surgical date, at which point presence or absence of SSI will be assessed by trained staff blinded to treatment allocation. The presence and number of emergency department visits for wound-related issues in the

interval will be specifically sought. Wounds deemed infected by the surgical team will be swabbed for culture and sensitivity including antibiotic resistance and treated with appropriate culture-directed oral or intravenous antibiotics. Data will be collected until the 90-day postoperative clinic visit. For patients not returning for the 90-day follow-up appointment, a telephone interview will be conducted by the research team to screen for potential wound complications not presenting to the clinical setting.

2.5 Outcomes and Data Collection

Baseline Data: The following data will be collected as baseline variables: Age, sex, BMI, preoperative ankle-brachial index (ABI), surgical indication (tissue loss, rest pain, claudication), nature of surgery (elective/urgent/emergent), presence or absence of comorbidities (diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, immunosuppression, autoimmune condition, smoking, chronic kidney disease, dialysis dependence), duration of dialysis dependence (continuous variable), required oxygen therapy (yes/no), presence of open wounds (yes/no), previous hospitalization within 30 days of surgery (yes/no), MRSA history (yes/no), pre-operative haemoglobin (continuous variable), 24hr serum glucose (continuous variable), white cell count (continuous variable). The following operative characteristics will be documented: conduit material (great saphenous vein, Dacron, PTFE, other vein), vein exposure (continuous/skip incision), vein configuration (in situ, reversed, nonreversed), bypass origin (common femoral artery, superficial femoral artery, profunda femoris artery, popliteal artery), bypass target (popliteal artery, anterior tibial artery, posterior tibial artery, peroneal artery, dorsalis pedis artery), bilateral groin incisions (yes/no), operative time (continuous variable), blood loss (continuous variable), quantity of blood products transfused (continuous variable), type of skin incision (oblique/vertical).

2.5.1 Outcome Measures

Primary Outcomes:

This pilot study will utilize a composite 90-day feasibility outcome to assess protocol applicability to the clinical setting and adherence. Components of the composite are described below with thresholds for feasibility.

1. Recruitment – consent rate of eligible patients as per inclusion/exclusion criteria - ≥80% of eligible patients
2. Successful randomization – Patients appropriately subjected to randomization at the time of operation - ≥80% of recruited patients randomized
3. Protocol adherence – Patients appropriately receive local antibiotics according to randomization scheme and undergo serial examinations per protocol - ≥80% of patients receive allocated treatment and complete follow-up
4. Successful Data Collection – All required data points are collected as defined in the trial protocol - ≥80% of randomized patients with complete data points
5. Contamination rate – Patients are withdrawn from the study protocol or crossed over into the opposite arm of the study based on patient or physician motivators - ≤20% of patients' data contaminated

Secondary Outcomes:

1. SSI occurring within 90 days of surgery
2. Length of post-operative stay in hospital
3. Emergency room visits within 90 days of surgery following discharge from hospital and before the first post-operative clinic visit
4. All-cause mortality within 90 days of surgery
5. Re-operation rate within 90 days of surgery
6. Major amputation (below or above knee) rate within 90 days of surgery
7. Seroma within 90 days of surgery

2.5.2 Definitions

Surgical site infections, as defined by the CDC, are classified based on depth of microbial invasion into superficial, deep and organ space. SSI are infections occurring within 30 days of surgery at the surgical site or within 1 year for deep and organ space infections if a prosthetic implant was placed. Specific criteria for diagnosis of SSI can be obtained

from the CDC[2,8]. Vascular surgical site infections in the groin often occur outside the 30-day window, therefore infections will be reported up to 90 days post-operatively. All SSI will be diagnosed by a surgical team member.

Tissue loss is defined as gangrene or cutaneous ulceration affecting a limb secondary to arterial occlusive disease. Redo surgery is defined as an operation occurring in a surgical field previously operated on. Dialysis dependence refers to ongoing hemodialysis or peritoneal dialysis secondary to end-stage renal disease (GFR <15mL/min/1.73m$^{2)}$. Diabetes mellitus includes those with either type I or II disease controlled with either oral hypoglycemic agents or insulin injection. Seroma is defined as a sterile fluid collection at the operative site identified on clinical examination (swelling, clear drainage, absence of cellulitis or purulence).

The Szilagyi classification is a system used to classify vascular surgical wounds following implant of a prosthetic graft based on extent of invasion. Infections are graded from I-III according to the following: I-infection involves only the epidermis and dermis; II-infection extends into the subcutaneous tissue but does not invade the arterial implant; III-the infection involves the vascular graft[9].

2.6 Statistical Analysis

2.6.1 Sample size

This study is a feasibility study that will allow calculation of an appropriate sample size for a full randomized controlled trial using the estimated effect size of the study. There are no studies using a similar protocol in the existing vascular surgery literature, however effect sizes from previous studies in cardiac, vascular, and orthopedic surgery have shown effect sizes of at least 0.2-0.3 for local antibiotic prophylaxis using vancomycin or gentamicin for SSI prophylaxis. Our recent RCT of negative-pressure wound therapy on vascular SSI in high-risk patients has given us a baseline 90-day rate of SSI following lower extremity bypass of 22%, which is consistent with prior literature.[34]

Whitehead et al. have summarized several methods used to select a pilot trial sample size that will provide a reasonable estimate of the mean and variance of the parameter of interest to allow calculation of sample size for a full-scale trial[56]. Using a conservative estimated effect size of 0.1-0.3 with alpha of 0.05, power of 0.80, a pilot trial with a minimum of 20 groins in each arm will be sufficient to estimate the effect size of topical antibiotics on SSI infection rate compared to control group patients.

2.6.2 Analysis

Data analysis will be performed using an intention to treat approach. Data will be presented as mean or median. Continuous variables will be compared using Student's t-test and categorical variables analyzed using Fisher's exact test or Chi-squared test as appropriate. All statistical tests will be two-sided.

2.7 Clinical Impact

This study is the first randomized controlled trial to address whether selective administration of intraoperative topical vancomycin and gentamicin-eluding sponge prophylaxis to patients at high-risk for surgical site infections following peripheral vascular surgery reduces SSI. This study is meant to refine the protocol and inform a sample size for a future larger multicenter study.

2.8 Ethics Approval

The Western University Research Ethics Board approved this study on March 3, 2020. All patients in the study received a physical letter of information and a discussion was held with the patient and/or appropriate substitute decision-maker where all questions were answered. A signed consent form was completed by each patient or appropriate substitute decision-maker.

Chapter 3

3. Results

Recruitment for the feasibility study began on March 3, 2020, following ethics approval and study registration with clinicaltrials.gov (NCT04238923). Summary of enrolment is show in Figure 1. The demographic characteristics of the cohort are displayed in Table 1. Patients in the topical antibiotics arm were older and less likely to be active smokers.

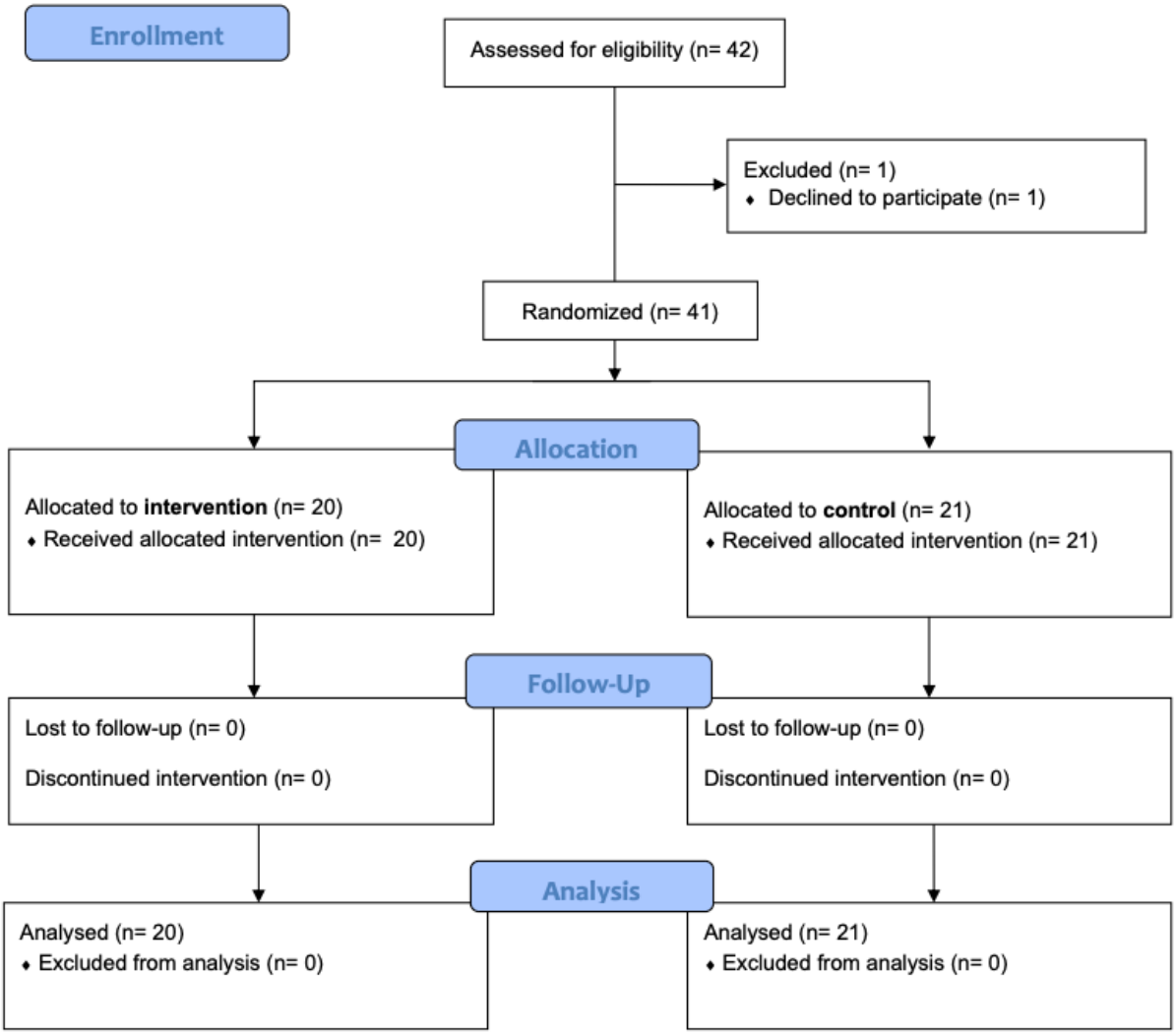

Figure 1. Summary of feasibility study enrolment.

Demographic	Total n=41 (%)	Control n=21 (%)	Topical Antibiotics n=20 (%)	p
Mean Age	70.4 +/- 7.5	66.4 +/- 5.9	74.8 +/- 6.8	<0.001
Female Gender	17 (31.7)	11 (52.4)	6 (30.0)	0.131
Mean BMI	27.8 +/- 5.8	27.6 +/- 6.7	28.1 +/- 4.8	0.827
Mean # of Criteria Met	1.8 +/- 0.8	1.6 +/- 0.7	1.9 +/- 0.8	0.425
Obesity	14 (34.1)	8 (38.1)	6 (30.0)	0.388
Diabetes Mellitus	23 (56.1)	10 (47.6)	13 (65.0)	0.464
Redo Surgery	18 (43.9)	10 (47.6)	8 (40.0)	0.982
Tissue Loss	15 (36.6)	5 (23.8)	10 (50.0)	0.169
Dialysis	0 (0)	0 (0)	0 (0)	NR
Mean preoperative ABI (right leg)	0.59 +/- 0.25	0.60 +/- 0.23	0.58 +/- 0.28	0.903
Mean preoperative ABI (left leg)	0.49 +/- 0.20	0.45 +/- 0.24	0.50 +/- 0.15	0.904
Coronary Artery Disease	17 (31.7)	6 (28.6)	11 (55.0)	0.169
Congestive Heart Failure	3 (7.3)	1 (4.8)	2 (10.0)	0.471
Chronic Obstructive Pulmonary Disease	10 (25)	4 (19.0)	6 (30.0)	0.306
Chronic Kidney Disease	2 (4.9)	2 (9.5)	0 (0)	0.170
Active Smoking	18 (43.9)	13 (61.9)	5 (25.0)	0.031
Recent Hospitalization	1 (2.4)	0 (0)	1 (5.0)	0.279
MRSA positive	0 (0)	0 (0)	0 (0)	NR
Claudication	7 (21.9)	3 (17.6)	4 (26.7)	0.538
Rest Pain	17 (31.7)	13 (61.9)	4 (20.0)	0.026
Tissue Loss	12 (37.5)	4 (19.0)	10 (50.0)	0.082
Emergency Surgery	5 (12.2)	3 (17.6)	2 (10.0)	0.349

Table 1. Demographic characteristics of the total, control and topical antibiotics patient cohorts. NR=Not reported due to zero event rate.

Forty-one groin incisions were randomized. Nine patients had bilateral groin incisions 4 of whom had one groin randomized to each group. The other 5 patients had both groins randomized to the control group in 2 cases and both groins to the topical antibiotics group in 3 cases (4 and 6 groin incisions respectively). There were 2 aorta-bifemoral artery bypasses (6.3%), 5 axillary-femoral artery bypasses (15.6%), 5 femoral-femoral artery bypasses (15.6%) and 13 infrainguinal bypasses (40.6%). Operative characteristics for these 32 procedures are shown in Table 2. Patients in the topical antibiotics group had a higher rate of blood product transfusion compared to the control group.

Operative Characteristic	Result n=41 (%)	Control n=21 (%)	Topical Antibiotics n=20 (%)	p
Great Saphenous Vein Conduit	7 (17.1)	3 (14.3)	4 (20.0)	0.538
Composite Conduit	5 (12.2)	3 (14.3)	2 (10.0)	0.737
Prosthetic Conduit	27 (43.9)	14 (66.6)	13 (65.0)	0.755
Oblique Groin Incision	12 (29.3)	5 (23.8)	7 (35.0)	0.538
Skipped Vein Harvest Incision	6 (14.6)	2 (9.5)	4 (25.0)	0.141
Subcuticular Suture Skin Closure	5 (12.2)	2 (9.5)	3 (15.0)	0.893
Mean Operative Time (minutes)	197.4	187.9 +/- 49.8	208.1 +/- 68.0	0.340
Blood Transfusion	7 (17.0)	2 (9.5)	5 (25.0)	0.047

Table 2. Operative characteristics of the total patient cohort. Results are presented as counts and percentages unless otherwise indicated.

3.1 Feasibility Outcomes

In general, thresholds for feasibility across the studied outcomes were met. These data are demonstrated in Table 3. Details pertaining to each outcome are provided below.

Feasibility Outcome	Result (%)
Recruitment	41 (97.6)
Randomization	41 (97.6)
Protocol Adherence	41 (100)
Data Collection	40 (97.6)
Data Contamination	2 (4.9)

Table 3. Feasibility outcomes of the recruited patient cohort.

3.1.1 Recruitment

The first patient was recruited on November 5, 2020 and the last patient was recruited on January 10, 2022. The COVID-19 pandemic caused major restrictions on research over the study period, as well as reductions in surgical volumes at our institution, resulting in significant disruption to the expected recruitment plan. 32 patients with 41 groin incisions

were recruited over the 14-month period, satisfying our minimum requirements for enrolment of 20 groins per arm.

One patient declined to participate in the study, he refused to provide any specific reason.

In general, patients had few concerns about participation in the study. Patient questions pertained mainly to whether they would have to return to the hospital for additional follow-up, compared to undergoing surgery without study participation.

3.1.2 Randomization

Randomization of the recruited cohort was successful in 97.6% of cases. Allocation was concealed in all cases by the randomization software. Randomization was carried out in the operating room by the member of the surgical team closing the incision. The consultant surgeon and any members of the surgical team expected to assess the groin incision for SSI were not in the operating room at the time of randomization and closure in all cases. All patients remained blinded to their treatment allocation as naturally they were unaware of the method of closure and application of topical agents.

One patient was randomized following induction of anesthesia; however, the anticipated procedure was abandoned due to inability to cross a common iliac artery occlusive lesion. The patient subsequently underwent a different operation 4 days later for which she was re-recruited and randomized according to protocol without concern.

3.1.3 Protocol Adherence

All randomized patients successfully had the protocol applied. For patients undergoing infrainguinal bypass using the ipsilateral great saphenous vein conduit harvested though a continuous incision, some concern was raised about how to best distribute the antibiotics along the incision. In these cases, the gentamicin-eluting sponge and vancomycin powder were applied along a 10-15cm segment of the incision centered on the groin crease, at the appropriate depth.

Four patients with 5 groin incisions (12.2% of the patient cohort) had the skin closed with subcuticular suture as opposed to staples, which was done to relieve short-term follow-up for suture removal, typically given long patient travel times to the hospital.

3.1.4 Data Collection

Data collection was complete in 97.6% of cases. All patients' incisions were monitored daily by the surgical team while in-hospital and reviewed in clinic at the appropriate 30 and 90-day follow-up appointments. One patient in the study group who underwent left axillary-femoral artery bypass, left femoral endarterectomy and left femoral-popliteal artery in situ bypass presented to the emergency department from home with vital signs absent on postoperative day 19 from suspected cardiac causes. Her data is censored at that date and did not contribute to the 90-day SSI rate. No patient was lost to follow-up.

3.1.5 Data Contamination

Data contamination was infrequent but occurred in the presence of other sources of infection outside the groin incision. One patient who underwent a femoral-tibial artery in situ bypass developed cellulitis at the distal leg incision prompting treatment with cefazolin for 7 days while in hospital. His groin incision eventually developed a grade II SSI following discharge. Another patient developed an SSI of the abdominal incision of an aorto-bifemoral bypass which was successfully treated by opening the incision, packing and broad-spectrum IV antibiotics. Her groin incisions remained infection-free throughout the study period. Both patients were in the control arm.

3.2 Surgical Site Infection and Clinical Outcomes

3.2.1 Surgical Site Infection

SSI occurred in 13 patients, representing 31.7% of the study patients. There were 6 superficial or grade I SSI, 6 deep or grade II SSI and 1 graft infection or grade III SSI. There were 8 SSI in the control arm (38.1%) and 5 in the topical antibiotics arm (25.0%), the difference was not significant (p=0.368). These results are displayed in Table 4.

Group	SSI n=41 (%)	p
Control	8 (38.1)	0.368
Topical Antibiotics	5 (25.0)	
Total	13 (31.7)	

Table 4. Overall SSI in the control and topical antibiotics cohorts.

Grade I SSI occurred in 3 control patients and 3 topical antibiotics patients. Grade II SSI developed in 4 control patients and 2 topical antibiotics patients. The single grade III SSI occurred in the control arm. Of the total 13 SSI, 1 was diagnosed in-hospital while the remaining 12 were identified between hospital discharge and the 30-day follow-up. No new infection was identified at the 90-day follow-up. All SSI were diagnosed by a member of the surgical team (senior resident or consultant). No patient required reoperation or amputation for infection. All SSI were managed with oral or intravenous antibiotic therapy, some cases had wound packing or negative pressure wound therapy. In the 9 patients with bilateral groin incisions, SSI developed in 7 of the 18 groin incisions (38.9%). Both groins developed SSI in 2 cases accounting for 4 grade II SSI, unilateral grade I SSI occurred in 3 cases. One of the 5 incisions closed with subcuticular sutures developed a grade I SSI (20%), this incision was in the experimental arm. A clinical summary of the patients in whom SSI occurred is presented in Table 5.

Patient	Operation	SSI Grade	Group	Management
4	Right iliac artery stent, femoral-tibial artery in situ bypass	1	Topical antibiotics	Culture negative, oral antibiotics
11	Femoral-femoral artery bypass	1	Control	Culture negative, oral antibiotics
12	Left femoral-popliteal artery in situ bypass	1	Control	Culture negative, oral antibiotics
24	Left extended profundaplasty, bilateral iliac artery stent	1	Topical antibiotics	Culture negative, oral antibiotics
26	Bilateral extended profundaplasty, bilateral iliac artery stent	1	Topical antibiotics	Culture negative, oral antibiotics
29	Bilateral extended profundaplasty, left iliac artery stent	1	Control	Culture negative, oral antibiotics
8	Right axillary-femoral artery bypass, right extended profundaplasty, right femoral-posterior tibial artery composite bypass	2	Control	Culture, negative, IV antibiotics, negative pressure wound therapy
9 (right groin)	Femoral-femoral artery bypass, right superficial femoral artery stent	2	Control	*S. aureus*, oral antibiotics, negative pressure wound therapy
9 (left groin)	Femoral-femoral artery bypass, right superficial femoral artery stent	2	Topical antibiotics	*S. aureus*, oral antibiotics, negative pressure wound therapy
18	Right femoral-anterior tibial artery in situ bypass	2	Topical antibiotics	*S. epidermidis*, IV antibiotics, negative pressure wound therapy
20 (right groin)	Right axillary-bifemoral artery bypass	2	Control	Culture negative, oral antibiotics
20 (left groin)	Right axillary bifemoral artery bypass	2	Control	Culture negative, oral antibiotics
27	Left extended profundaplasty, left iliac artery stent	3	Control	*P. aeruginosa*, oral antibiotics and wound packing

Table 5. Clinical details of patients developing SSI.

3.2.2 Length of Stay, ED Visits, Reoperation, Amputation, Mortality, Seroma

Additional clinical outcomes are summarized in Table 6. There were no significant differences between the control and topical antibiotics groups with respect to length of stay, emergency department visits, reoperation, amputation or mortality. One patient in

the experimental arm presented to the emergency department with vital signs absent on postoperative day 19 from suspected cardiac causes. An autopsy was not performed. There were no concerns with respect to her surgical incisions reported the emergency physicians. She represents the lone mortality. Seroma occurred in 4 patients overall, 1 in the control arm and 3 in the topical antibiotics arm. One patient with a seroma in the topical antibiotics group developed a grade 2 SSI treated with IV antibiotics and negative pressure wound therapy.

Outcome	**Total n=41 (%)**	**Control n=21 (%)**	**Topical Antibiotics n=20 (%)**	**p**
Length of stay	5.6 +/- 4.3	4.8 +/- 2.5	6.6 +/- 5.6	0.234
Emergency department visit	0 (0)	0 (0)	0 (0)	NR
Reoperation	0 (0)	0 (0)	0 (0)	NR
Amputation	0 (0)	0 (0)	0 (0)	NR
Mortality	1 (2.4)	0 (0)	1 (5.0)	0.300
Seroma	4 (9.8)	1 (4.8)	3 (15.0)	0.269

Table 6. Secondary clinical outcomes in the total, control and topical antibiotics cohorts. NR=Not reported due to zero event rate.

Chapter 4

4. Discussion

4.1 Feasibility

SSI is an important and prevalent complication following vascular operations performed through groin incisions, with significant morbidity and healthcare resource demands associated with its occurrence. The incidence of SSI after arterial surgery in the literature varies but is usually reported between 10-20% based on both retrospective registry and prospective trial data[11-16]. Patients at highest risk of SSI can be identified based on clinical factors in the preoperative setting, as has been shown in multiple prior reports. Patients who are obese, diabetic, on dialysis, have tissue loss or are undergoing redo surgery are at especially high risk of developing SSI following arterial surgery involving a groin incision[10,12,13,15,26,27,28]. The incidence is influenced by the duration of follow-up, many patients present with SSI after hospital discharge and graft infections can present months to years after surgery. This study effectively captured a high-risk cohort for SSI, as evidenced by the 31.7% incidence of SSI in the overall sample. This result is in keeping with prior estimates of SSI in high-risk cohorts. Given that this incidence is much higher than CDC standards for other clean operations of ~5%, additional prophylactic measures in these patients seems warranted. This event rate would also inform any future trial looking at this high-risk group.

Feasibility was achieved based on our pre-defined thresholds for all aspects of the study. These included >80% recruitment, randomization, protocol adherence and data collection as well as <20% data contamination. Based on these results, a larger trial is indeed feasible.

Recruitment was successful in all but one case, or 97.6% of cases were recruited. This highlights that most patients are accepting of the rationale for the study and understand that risks of participation are minimal. The one patient who declined to participate refused to enter the study before any information about the study was relayed to him, therefore his refusal was probably not due to concerns about anything specific to the study and more likely reflect the patient's general attitudes towards medical research. The

COVID-19 pandemic did result in a lower than anticipated rate of recruitment as a result of research restrictions and operating room closures. As these restrictions are lifted, it is probable that recruitment of a minimum 2 patients per week into a full-scale trial at this institution is reasonable. Recruitment for a larger trial is thus feasible.

Randomization was successfully achieved in 97.6% of cases. One patient was randomized prior to revascularization, and her operation ultimately was abandoned, and a different approach was used to revascularize her lower extremity. A groin incision was used for this operation and the patient was randomized again. We have since modified the protocol such that randomization occurs in the operating room immediately prior to closure, to limit similar incidents. Allocation was concealed in all cases using an online algorithm for randomization and blinding was maintained for the outcome assessors and patients. Randomization for a full-scale trial is clearly feasible.

The protocol was appropriately followed in all cases. Participating surgeons were already familiar with the use of local vancomycin powder for SSI prophylaxis. The addition of the gentamicin-eluting sponge was regarded as straightforward and intuitive. The participating surgical team members did not report any difficulty applying the product after one or two uses experience. This suggests that the protocol can feasibly be adhered to for a larger trial.

Data collection was complete in 97.6%. The one patient with incomplete data presented from home vital signs absent on postoperative day 19 from probable cardiac causes. She had no evidence of wound related complications in-hospital following surgery. All other patients completed the 30-day and 90-day in-person follow-up regimen. The 90-day follow-up period was deemed prudent based on prior literature reported delayed appearance of vascular surgical site infection, however, in this study all SSI were identified by the 30-day follow-up. While the 90-day follow-up should be maintained to ensure detection of these delayed infections in the full-scale trial, attention should be directed to the early follow-up period when most SSI will present. No patient required telephone follow-up for SSI monitoring. This is partly a result of the fact that these study

follow-up timepoints coincide with standard in-person follow-up regimens after lower extremity revascularization. The ability to directly inspect the incisions for SSI at each timepoint would add methodological strength to a full-scale trial. In addition, a large proportion of the SSI were diagnosed on clinical grounds with negative cultures thus making the direct visualization of the wounds by the assessor critical in accurately capturing the endpoints. It was unclear for this feasibility study if all patients would comply with the in-person follow-up. The telephone follow-up questionnaire was thus designed to improve the follow-up rate, allowing identification of patients who clearly needed to be reviewed in-person if they reported incisional concerns over the phone. Given our data collection rate of 97.6%, this aspect of the trial is feasible, and the telephone follow-up could likely be omitted from a larger trial.

Data contamination in the form of a potential cointervention bias occurred in 2 cases. This occurred when these patients developed a concurrent infection necessitating antibiotic treatment during the follow-up period. One case included a superficial SSI of the distal leg incision of a femoral-tibial artery bypass, not involving the groin, the other case was a deep SSI of the abdominal incision of an aorta-bifemoral bypass without involvement of the groin incisions. Both patients were prescribed systemic antibiotics during the follow-up period. This may have influenced their likelihood of developing an SSI. Three groin incisions in these 2 patients were all randomized to the control arm. Concurrent infections are a common problem in this patient population, and it should be anticipated that such infections will occur in the larger trial and should be appropriately treated with systemic therapy. There is no reason why concurrent infection would disproportionately affect one group versus the other. It is therefore unlikely that such infections would bias the results of a larger trial in favour of either group. With our groin SSI rate of 31.7%, it is unlikely that treatment of these infections is suppressing a significant number of groin SSI by administration of systemic antibiotic prophylaxis. The data contamination rate of 4.9% is therefore acceptable and supports feasibility of a full-scale trial of this novel closing protocol.

4.2 Clinical Outcomes

This study is a feasibility study, and as such, it is not designed to detect significant differences in the clinical outcome of SSI between the standard closure and gentamicin-eluting sponge with vancomycin powder groups. A few important comments can be made about the clinical data accrued in this study. SSI occurred in 31.7% of the total patients in this study. This is consistent with prior reports of SSI in high-risk cohorts undergoing vascular surgery performed through a groin incision. The infection rate was lower in the patients undergoing closure with topical antibiotics compared to standard closure, 25.0% versus 38.1% (p=0.368), an absolute risk reduction of 13.1% and relative risk reduction of 34.4%. This suggests that our protocol may reduce the risk of groin wound infections but this would need to be confirmed by a larger, appropriately powered, trial. This was despite a statistically higher rate of blood transfusion, a known predictor of SSI, in the topical antibiotics cohort compared to the control group (33.3% versus 5.9%, p=0.047)[10,13]. There is no physiologic rationale in which the closing protocol would account for the higher rate of bleeding in the experimental group. In fact, the gentamicin-eluting sponge uses collagen as a carrier, which has known hemostatic properties. Furthermore, the rate of reoperation was 0, suggesting that the blood loss resulting in these transfusions was not related to the surgical site. This difference in transfusion rate is most likely a result of intraoperative blood loss and baseline patient comorbidities.

The distribution of infection severity was even for grade I SSI (3 each), however grade II or III infections occurred more frequently in control group patients compared to experimental group patients (5 versus 2), suggesting that severity of infection is an important component of the SSI outcome to assess in the larger trial. All SSI were managed successfully with systemic antibiotics and appropriate wound care.

As expected, given the feasibility design of this study, no differences in emergency department visits for wound related issues, reoperation, amputation and mortality were noted. Of note, the event rate for these outcomes was 0 except for the single mortality. Length of stay was about 5-6 days overall and similar between groups. In this study 4 seromas (9.8%) developed, 3 (15%) seromas occurred in the topical antibiotics arm and only 1 (4.8%) in the control arm. This difference was not statistically significant

(p=0.269), but notable. One patient with a seroma did develop a deep SSI, it is unknown whether occurrence of this SSI was influenced by the presence of the seroma. It is possible that the presence of the sponge may increase seroma formation as it increases the potential for dead space in the wound which may potentiate seroma formation. This observation warrants further evaluation in the larger trial.

Overall, the clinical outcomes obtained from this feasibility sample support the rationale and design of the study. The event rate of 31.7% for SSI is consistent with our predictions and the effect size of 13.1%, although slightly lower than anticipated, suggests that this novel closing protocol may provide a meaningful benefit against SSI in these high-risk patients.

4.3 Future Directions

This feasibility study was not powered to detect significant differences between the control and topical antibiotics groups, however, the incidence of SSI in this high-risk cohort can be used to estimate the sample size for a full-scale randomized controlled trial. Our actual effect size of 13.1% between study arms in favour of local application of a gentamicin-eluting sponge and vancomycin powder provided a relative risk reduction for SSI of 34.4%, consistent with our estimate of 0.25-0.30 based on existing non-vascular surgery literature. Our study sample randomized >20 incisions to each arm, in accordance with the recommendations of Whitehead et al. for sample size calculation of a full-scale trial based on a pilot study with an effect size 0.1-0.3[56]. Using the effect size of 13.1% from this study a full randomized controlled trial could be undertaken with 196 patients in each group to achieve power of 0.8 at alpha 0.05[57].

The full randomized controlled trial of topical gentamicin and vancomycin versus control closure of high-risk groin incisions would benefit from subgroup analyses to assess the contribution of certain clinical factors to the incidence of SSI. For example, type of closure (subcuticular suture versus staples) has previously been shown to affect the incidence of SSI and should be controlled for in the definitive study. Additionally, stratifying diabetic patients based on hemoglobin a1c levels and active smokers by

urinary cotinine levels may allow for more robust comparisons between experimental and control groups by controlling for these known risk factors for SSI. Serum monitoring of gentamicin and vancomycin levels in patients with known renal failure should also be considered to limit the possibility of adverse effects related to topical antibiotic use.

4.4 Study Limitations

This study was designed as a feasibility study; therefore, an inherent weakness is that there is insufficient power to detect significant differences in the clinical outcomes of interest. Nevertheless, feasibility studies allow the study protocol to be tested in a real-world setting. The event rate for the outcome of interest, in the appropriate population, can be assessed in the feasibility trial thereby allowing for accurate determination of sample size in the larger trial. This increases the reliability of the full-scale trial results[34].

Another limitation of this study is that diagnosis of SSI does not rely on a single objective clinical measure for its diagnosis, rather a constellation of symptoms, signs and laboratory data[2,8]. Diagnosis of SSI is thus subject to bias by the outcome assessor. This is particularly germane in the context of negative wound cultures in 70% of the SSI in this study, making the clinical judgment of the provider the critical factor in determining whether SSI is present. Given that there exists no method of SSI diagnosis more accurate than clinical examination supported by laboratory, imaging and culture results in the appropriate setting, this is not a unique weakness to this study and is an inherent component of essentially all studies examining SSI.

The COVID-19 pandemic undoubtedly had an impact on the recruitment rate of this study. With research restrictions and operating room closures, the ability to recruit the patients suitable for study was limited. Despite this, we were able to recruit sufficient patients to obtain a reasonable estimate of SSI incidence and the effect of topical antibiotic use in this setting, based on prior guidelines for feasibility studies. With many of these restrictions now lifted, the recruitment rate for a full-scale trial would be expected to increase substantially.

4.5 Conclusion

This study assessed whether a double-blinded randomized controlled trial comparing standard groin closure methods to groin closure with local gentamicin-eluting collagen sponge and vancomycin powder application for SSI prophylaxis in high-risk patients could feasibly be conducted at our institution. The results of this feasibility study suggest that indeed such a trial is feasible and provide preliminary data on the incidence of SSI in the control and topical antibiotics groups, this allows an accurate sample size for the full-scale trial to be determined.

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Appendices

Appendix A: Western Research Ethics Board Approval

Western Research

Date: 3 March 2020

To: Dr. Luc Dubois

Project ID: 115156

Study Title: Topical Gentamicin and Vancomycin for Surgical Site Infection Prophylaxis in Patients Undergoing High-Risk Vascular Surgery

Application Type: HSREB Initial Application

Review Type: Delegated

Meeting Date: 25/Feb/2020 13:00

Date Approval Issued: 03/Mar/2020 08:39

REB Approval Expiry Date: 03/Mar/2021

Dear Dr. Luc Dubois

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Data points Vanco Gent REM	Other Data Collection Instruments		
Protocol Vanco G V3	Protocol	26/Feb/2020	3
Vanco G 90 day phone call script V2	Other Data Collection Instruments	26/Feb/2020	2
Vanco Gent LOI V2	Written Consent/Assent	07/Feb/2020	2.0
vanco:gent 90 day phone Qs	Other Data Collection Instruments		

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Vancomycin Budget DLEBLANC-2	Study budget	05/Feb/2020	1

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geogehgan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Appendix B: Letter of Information and Consent Form

LETTER OF INFORMATION AND CONSENT FORM

Title of Study: Topical Gentamicin and Vancomycin for Surgical Site Infection Prophylaxis in Patients Undergoing High-Risk Vascular Surgery

Principal Investigator: Dr. Luc Dubois

Co-Investigators: Dr. Dominic, LeBlanc, Dr. Guy DeRose, Dr. Adam Power, Dr. Audra Duncan

Sponsor: This study is sponsored by The Department of Surgery at Western University

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Introduction:

You are being invited to take part in this clinical research study because you have been diagnosed with peripheral artery disease (PAD) that warrants surgical treatment. In PAD, arteries that deliver blood to the leg and foot are narrowed or blocked by plaque buildup (atherosclerosis). PAD can cause pain in the foot or leg even when sitting or lying at rest; it also can cause foot and leg ulcerations, and can sometimes lead to gangrene and loss of the leg.

PAD is usually treated by operations that increase blood flow to the leg and foot, in order to relieve these symptoms, heal the ulcers, and preserve the limb. Your surgeon has determined that an operation that creates a bypass around the blockage is appropriate for your case. Given your history of diabetes, dialysis dependence, elevated body mass index (BMI) or previous vascular surgery, you are at a higher risk for a surgical site infection (SSI) compared to other patients undergoing surgery. SSI increase the risk that your bypass will fail, that you will ultimately require an amputation and increase the amount of healthcare resources you require to recover from surgery. Intravenous antibiotics are a routine part of SSI prevention in surgery, however there is evidence to suggest that administering antibiotics directly on the surgical site at the time of surgery provides additional benefit.

This letter of information and consent form tells you about the study and includes information about the reason why the study is being done, what will happen to you if you take part in the study, and the possible risks and benefits of this study. Please take time to read this document carefully and please feel free to talk about it with your partner, family members, family doctor or others. If you choose to take part in this study, you will be asked to sign the consent form. You will get a fully signed and dated copy of this information letter and informed consent form.

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. Your other medical care will stay the same whether or not you join the study. We will let

you know about any new information that becomes available during the study that may affect whether you want to continue to participate. If you join the study, the study staff will inform your family doctor about your participation.

Your study doctor will also talk to you about the information in this letter of information and consent form in detail. Please ask your study doctor or the study staff to explain any words or facts that you do not understand or if you would like more information.

What is the purpose of this study?

The purpose of the study is to learn whether applying the antibiotics vancomycin and gentamicin to the surgical wound at the time of surgery helps prevent SSI.

This study is a small scale, or pilot study, of a larger trial we will be conducting to assess the effect of topical gentamicin and vancomycin. About 100 patients from London Health Sciences Centre will be recruited into the pilot study. The results of the pilot study will help design the larger scale trial.

Are there any benefits from participating in this study?

You may benefit from a reduction in SSI if randomized to the experimental arm that will receive topical antibiotics. not benefit from being in this research study. We hope to gather information that will inform vascular surgeons about the optimal method to prevent SSI in the future.

Which treatment will I receive and when will I know?

Half of the participants in this study will receive topical antibiotics and half will receive standard wound care. The assignment of treatment is purely by chance (50:50, just like a coin toss). Your study doctor cannot tell you in advance which treatment you will be assigned, as this is only determined after you are enrolled in the study. So, if you enroll in this study, you should be prepared to receive either treatment, topical gentamicin and vancomycin or no topical antibiotics.

Study Procedures

Patients who qualify for this study will be randomized (assigned by chance like the flip of a coin) to get one of the following study treatments:

- **Treatment 1**: Topical vancomycin 1g, applied as a paste and gentamicin-eluting collagen sponge (Collatamp G) applied to the bed of the surgical groin wound prior to closure, along with standard wound closure protocols.
- **Treatment 2**: Standard closure of the surgical incision (with sutures +/- staples).

You will have a 50% chance of getting treatment 1 (topical gentamicin plus vancomycin) and a 50% chance of getting treatment 2 (standard closure).

You will not know which treatment you received, nor will the study doctor assessing your wounds for infection. However, your surgeon will know which treatment you are getting and your study doctor can find out if there is an emergency or if it is needed to know for your health.

You will then be asked to come back to the clinic for evaluation after 1 month and 3 months. These visits will coincide with your standard of care visits with your doctor after your procedure. You will also be contacted by phone at 90 days by a study team member to discuss your current symptoms.

Prior to your surgical procedure, you will have routine pre-operative tests (part of standard care), as determined by you and your study doctor.

All other aspects of your surgical, including admission to the hospital, hospital stay, anesthesia, and some of your post-operative visits are part of your routine care and not performed specifically for the purposes of this research study.

Specific visits for the research study are described below:

Baseline (Initial Visit: approximately 2 hours): You will be asked to:

- Sign informed consent.
- Review the results of imaging tests (an ultrasound, angiogram, CAT scan, or Magnetic Resonance Scan) that you have had recently (standard care).
- Review your medical history, peripheral vascular history, and current medications.
- Have a physical examination.
- Have a hemodynamic assessment (a non-invasive method to measure pressure in the blood vessels by measuring blood pressures in your arms and legs with ultrasound)
- Have a blood draw for cell counts and glucose levels. Less than 1 teaspoon of blood will be collected for these tests.

Procedure Visit: You will be asked to return to this hospital after baseline visit to have surgery with topical gentamicin and vancomycin (if you are assigned to Group A) or standard closure (if you are assigned to Group B). Information about your operation and stay in hospital including: operative details, length of stay, complications will be recorded as part of the study. During the first two days after your surgery, your regular daily bloodwork will include blood levels of gentamicin and vancomycin.

In-Person Follow-Up Study Visits: (approximately 2 hours each).
You will be asked to return for study visits 30 days after the procedure and at 3 months. Many of these visits will coincide with your standard care post-surgery visits. At each visit, we will collect information about your:

- Current signs and symptoms.
- Current medications.
- Physical examination, including inspection and palpation of the wound and revascularized limb, body weight, heart rate, and blood pressure.
- Hemodynamic assessment (a non-invasive method to measure pressure in the blood vessels by measuring blood pressures in your arms and legs with ultrasound) at 30 days after the procedure, and at 3, 6, and 12 months.

In addition, you may be asked to do the following at any follow-up visit:

- Provide a specimen from the wound via a swab to assess for bacterial growth in a laboratory.
- Give approximately 1 teaspoon of blood for blood cell counts.
- Schedule additional imaging tests including an ultrasound or CAT scan.

- Inform us about your use of healthcare services since the procedure.

The purpose of these assessments would be to determine if you have developed an SSI or a complication related to an SSI.

Telephone Follow-Up Study Visits: (approximately 30 minutes each):
In the even that you are unable to return for either follow-up appointment, you will have an appointment that will be conducted over the telephone. We will collect information about:

- Your symptoms.
- Medications you are taking.

How is this different from what will happen if I do not participate in this research?
The standard of care for your condition can be either standard wound closure with the addition of topical antibiotics if the risk of infection is thought to be high. The treatments offered in this research project are available to you as deemed necessary by you surgeon without enrolling in this study.

If you enroll in this study, we will ask you to complete additional visits and provide information on your signs and symptoms, use of medications, quality of life, and use of health care services. Your post-operative bloodwork will include blood gentamicin and vancomycin levels, which is not routine after surgery. You may have samples collected form the wound more often than if you were not in the study. You may undergo more imaging tests, such as ultrasounds or CAT scans in follow-up.

What are the risks involved with being enrolled in this study?
There are risks associated with any operation or procedure. We cannot be sure how your body may respond. The study doctor will discuss possible difficulties and the chances that they might happen.

There is a chance that you may experience one or more of the risks and/or discomforts listed below from the use of topical vancomycin or gentamicin. These may be considered in terms of local side effects and whole-body, or systemic, side effects. Systemic side-effects are more likely if the medication is absorbed into the bloodstream, therefore we will monitor your blood levels of these drugs after surgery.

The revascularization operation you will receive carries its own specific risks not specific to the study that your surgeon will discuss with you before they perform the procedure on you. You may also experience a risk that is currently unknown.

All of the following adverse events are reported as very rare (less than 1 in 10 000 people undergoing topical treatment). Risks of whole-body side effects of both vancomycin and gentamicin may be increased in the presence of pre-existing kidney failure.

Potential limb-related risks of topical vancomycin include:

- wound dehiscence
- hernia of the wound

Potential limb-related risks of topical gentamicin include:

- no reported adverse events to date

Potential whole-body related complications associated with vancomycin:

- anaphylaxis
- “red man” syndrome: flushing, wheezing, shortness of breath, low blood pressure
- kidney failure
- hearing loss
- vertigo
- dizziness
- tinnitus
- decrease in neutrophils, a component of blood involved in fighting infection
- decrease in platelets, a component of blood involved in forming blood clots and preventing bleeding
- gastrointestinal symptoms related to *Clostridium difficile* infection

Potential whole-body related complications associated with gentamicin:

- kidney failure
- electrolytes abnormalities
- vertigo
- dizziness
- tinnitus
- hearing loss
- altered mental status
- headache
- numbness and tingling in the extremities
- weakness
- convulsions
- respiratory depression
- pulmonary fibrosis
- swelling of the larynx causing difficulty breathing
- high or low blood pressure
- nausea and vomiting
- decreased appetite and weight loss
- enlargement of the liver or spleen
- elevated markers of liver injury in the blood
- rashes with or without itching
- decreased blood cell counts
- hair loss
- joint pain

Study visit evaluations may be inconvenient. There may be questions that make you feel uncomfortable. If there are any questions that you do not want to answer, you will not be required to answer them.

Risks associated with drawing blood include discomfort and/or bruising at the puncture site. Rarely, infection, excess bleeding, clotting or fainting may occur.

There may be additional risks or discomforts that are not known at this time.

Reproductive Risks and Risks to Pregnant Women:
The risks of topical gentamicin and vancomycin application to pregnant or breast-feeding women are unknown. If you are a woman and are currently pregnant or breast-feeding a child, or if you intend to become pregnant in the next 30 days, you cannot participate in the study. If you are a woman of childbearing age, your study doctor will conduct a pregnancy test at the baseline visit. The pregnancy test result must be negative in order to enroll in the study. If you miss a period or think you may be pregnant, you should notify the study doctor immediately. You may have to withdraw from the study.

Other important items you should know:
• Your decision whether or not to participate in this study, or a decision to withdraw from the study, will not involve any penalty or loss of benefits to which you are entitled.

• You will not receive any compensation if the results of this research are used towards the development of a commercially available product.

• **Withdrawal from the study:** You may be withdrawn from the study if, in the judgment of your study doctor, it is in your best interest. You may be withdrawn from this study by the study sponsor.

After withdrawing, no new information about you will be collected for study purposes unless the information is about an event that is related to the study. If you are unwilling to have your medical records reviewed through the end of the trial period, please contact Dr. Audra Duncan and let her know that you are withdrawing your permission. [
Publically available data, may be used to collect information about your vital status at the end of the trial.

• **Funding:** The Department of Surgery at Western University here, in London, Ontario has provided funding for this study.

How will my privacy be protected?
During your participation in the study, your health information, such as information on your medical condition, will be collected and stored on paper or electronically stored in medical records at the study doctor's office. This health information will be protected against unauthorized access and kept confidential. Your data will be coded, instead of using your name, to keep your identity confidential. The list linking the code with your name is kept at the study doctor's office.

During and after the study your encoded data may be provided to the sponsor, its partners, that are involved in the research and development of the study drug, their group companies and their contract service providers (e.g. laboratories).

The encoded data will be used to report side effects to the ethic committees, Health Canada and/or other foreign government agencies, as required by laws and regulations. The encoded data will be analysed to determine the results of the study, publish the results in scientific articles or presentations, and submit them to Health Canada and/or other foreign government agencies to help them decide if the study drug can be approved to go on the market.

To make sure the study is being done properly; your research study file as well as your medical file could be checked by a person authorized by Western University Health Sciences Research Ethics Board, or by the institution, or by Lawson Health Research Institute Quality Assurance, by a person authorized by groups such as Health Canada, and the United States Food & Drug Administration (FDA). To the extent possible, any information about you that leaves LHSC will have all identifying information removed. These people and groups are obliged to respect your privacy.

If you are hospitalized for during the study, your study doctor will have to collect all information from the respective hospital or medical institution.

Any published information including reports and articles about the study will not include your name or any information that could personally identify you. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

You may change your mind and revoke (take back) this permission to use your health information at any time. To revoke this permission, you will need to contact your study doctor. However, if you revoke this permission, you will no longer be a participant in the study.

Also, even after your participation in the study ends, your health information cannot be removed from the study data and Authorized Personnel may continue to use and disclose the health information they obtained during the study as described in this consent form. No additional information can be collected without your consent.

You do not have to sign this consent form if you do not agree with the uses and disclosures of your health information described above. However, if you do not sign this consent form, you will not be able to participate in the study.

Will the study cost me anything or do I receive payment or compensation?
There will be no extra costs to you for your tests, examinations or medical care required as part of this study. Any costs incurred as a direct result of your participation, e.g. travel expenses to a maximum of $50.00 per visit for transport, parking, and meals will be reimbursed. . If you live more than 100 miles away from the study site or on a case by case basis, you will receive $100.00 (instead of $50.00) upon successful completion of each study visit for travel expenses. You will not be paid for taking part in this study.

What happens if I get sick or hurt from participating in this study?
In the event of physical injury or physical illness resulting from your participation in this study, your provincial healthcare should cover the costs of medical care and treatment.
The study sponsor, the hospital, and the study doctor make no commitment to compensate you for any injury, nor for any additional expenses that you may have because of this study. Nevertheless, you do not waive any legal rights by participating in this study nor do you release the study doctors or the hospital from responsibility for their negligence. If you think that you have suffered a research related injury, let the study doctor know right away.

Whom should I call with questions about this study?

Please contact the study staff if you have any questions about this study, its procedures, risks and benefits, or alternative courses of treatment or in case of emergency.

Will information about this study be available online?
A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results.

CONSENT

Title of Study: Topical Gentamicin and Vancomycin for Surgical Site Infection Prophylaxis in Patients Undergoing High-Risk Vascular Surgery

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

SIGNATURES

Research Participant:

_____

_____

Participant's Signature and Date PRINTED NAME

Researcher or Designee:
I have given this research subject information about this study that I believe is accurate and complete. I have answered and will answer all questions to the best of my ability. I will inform the subject of any changes in the procedures or changes in the risks and benefits if any should occur during the study. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

_____

_____

Researcher or Designee Signature and Date PRINTED NAME

Curriculum Vitae

DOMINIC LEBLANC

EDUCATION

London Health Sciences Centre

PGY-4 Vascular Surgery 2018-present

Schulich School of Medicine and Dentistry 2014-2018

Doctor of Medicine Class of 2018

The University of Western Ontario 2009-2018

Bachelor of Medical Sciences

Honors Specialization in Biochemistry, Major in Medical Sciences

ABSTRACTS, PRESENTATIONS AND PUBLICATIONS

LeBlanc D, Phares P, Smith S, Landau J, Power A, Duncan A, DeRose G, Dubois L. Retropubic femoral-femoral bypass has superior long-term patency, freedom from major adverse limb events, and fewer graft infections when compared with grafts tunneled subcutaneously.

- Abstract submitted to 2022 Canadian Society of Vascular Surgery Annual Meeting, September 9-10, 2022.

Rockley M, Radonjic A, **LeBlanc D**, Jetty P. The Futility of Surveillance for Old and Small Aneurysms. J Vasc Surg. 2020 Jul;72(1):162-170e1

Kuper T, Federman N, Sharieff S, Tejpar S, **LeBlanc D**, Murphy P, Parry N, Leeper R. Chest Tube Insertion Among Surgical and Non-Surgical Trainees: How Skilled Are Our Residents? J Surg Res. 2020 Mar;247:344-349. doi: 10.1016/j.jss.2019.10.010. Epub 2019 Nov 21.

LeBlanc D, Chu M, Duncan A. Single-stage Hybrid Repair Of A Thoracoabdominal Aortic Aneurysm Complicated By Chronic Type B Aortic Dissection And Kommerell's Diverticulum Via Simultaneous Median Sternotomy And Laparotomy. 48th Society of Clinical Vascular Surgery Annual Symposium, March 14-18, 2020.

Hossain S, **Leblanc D**, Farber A, Power AH, DeRose G, Duncan A, Dubois L.

Editor's Choice - Infrainguinal Bypass Following Failed Endovascular Intervention Compared with Primary Bypass: A Systematic Review and Meta-Analysis**.** Eur J Vasc Endovasc Surg. 2019 Mar;57(3):382-391. doi: 10.1016/j.ejvs.2018.09.025. Epub 2018 Nov 2.

LeBlanc D, Power AH, DeRose G, Duncan A, Dubois L. Patient satisfaction with the consent discussion is not improved by showing patients their computed tomography or angiography images before they undergo vascular surgery. J Vasc Surg. 2018 Nov;68(5):1517-1523.e3. doi: 10.1016/j.jvs.2018.02.029. Epub 2018 May 18.

AWARDS AND ACCOLADES

Ontario Graduate Scholarships in Science and Technology 2021

Awarded for MSc in Surgery project, "Topical Gentamicin and Vancomycin for Surgical Site Infection Prophylaxis in Patients Undergoing High-Risk Vascular Surgery".

Value: $15000

Western University Department of Surgery Resident Research Grant 2019

Awarded for MSc in Surgery project, "Topical Gentamicin and Vancomycin for Surgical Site Infection Prophylaxis in Patients Undergoing High-Risk Vascular Surgery".

Value: $5000

Kenneth A. Harris Vascular Surgery Award 2018

Awarded annual to the undergraduate medical student at the completion of fourth year who has excelled in Vascular Surgery during their clerkship rotation and four years of undergraduate medical education.

Value: $1300

J.B. Campbell Memorial Scholarship in Medicine 2018

Awarded to a medical student who has shown outstanding proficiency in Medicine and Clinical Medicine in the final two years of the MD program.

Value: $400

Class of 1951 Frank R. Clegg Memorial Award 2018

Awarded annually to the medical student at the end of the clinical clerkship achieving the

best balance of high academic standing and those qualities of compassion and personal commitment generally regarded as essential to fulfilment of a role as a good physician, as judged by the Department of Family Medicine, Medicine, Obstetrics and Gynaecology, Paediatrics, Psychiatry and Surgery.
Value: $1200

Society for Vascular Surgery Medical Student Travel Scholarship 2017
Awarded to medical students aspiring to pursue vascular surgery as a career with funding to attend the Vascular Annual Meeting and participate in specific educational programming Allocated based on statement of interest in video format
Value: $765

Western Undergraduate Surgical Education Committee Certificate of Merit 2017
Achieved the highest standing among the clerks at London Health Sciences Centre, Victoria Hospital during the surgery clerkship period of Nov 21, 2016-Feb 19, 2017

Horace and Clarice Wankel Memorial Award 2016
Awarded to a Summer Research Training Program student demonstrating special interest in cardiovascular diseases
Value: $150

J.A.F Stevenson Award (Faculty Association Scholarship) 2016
Achieved the highest overall marks in the first year of the Doctor of Medicine Program
Value: $1000

J.B Campbell Memorial Scholarship in Heart and Circulation 2015
Achieved the highest mark in the Heart and Circulation block.

Value: $400

Patient-Centered Clinical Methods Year 1 Honors 2015
Awarded to first year Schulich medical students achieving ‘Pass with Honors’ in all four components of the full-year clinical methods course

Helen Atfield White Scholarship 2014
Awarded to the undergraduate student from Western registering in year 1 of the Schulich School of Medicine with the highest average in the previous year's work. Value: $450