Prevention of infection in peripheral arterial reconstruction: A systematic review and meta-analysis

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Objective: The aim of this systematic review and meta-analysis was to determine the effectiveness of perioperative strategies to prevent infection in patients undergoing peripheral arterial reconstruction.

Methods: All randomized controlled trials (RCTs) evaluating measures intended to reduce or prevent infection in arterial surgery were identified through searches of the Cochrane Peripheral Vascular Diseases Group specialized trials register, the Cochrane Central Register of Controlled Trials (CENTRAL), and reference lists of relevant articles. Two authors independently selected and assessed the quality of included trials. Relative risk (RR) was used as a measure of effect for each dichotomous outcome.

Results: The study included 34 RCTs. Of these, 22 were trials of prophylactic systemic antibiotics, 3 of rifampicin-bonded grafts, 3 of preoperative skin antisepsis, 2 of suction wound drainage, 2 of minimally invasive in situ bypass techniques, and individual trials of intraoperative glove change and wound closure techniques. Wound infection or early graft infection outcomes were recorded in all trials. Only two trials, both of rifampicin bonding, followed up graft infection outcomes to 2 years. Prophylactic systemic antibiotics reduced the risk of wound infection (RR, 0.25; 95% confidence interval [CI], 0.17 to 0.38) and early graft infection in a fixed-effect model (RR, 0.31; 95% CI, 0.11 to 0.85, P = .02). Antibiotic prophylaxis for >24 hours appeared to be of no added benefit (RR, 1.28; 95% CI, 0.82 to 1.98). There was no evidence that prophylactic rifampicin bonding to Dacron grafts reduced graft infection at 1 month (RR, 0.63; 95% CI, 0.27 to 1.49), or 2 years (RR, 1.05; 95% CI, 0.46 to 2.40). There was no evidence of a beneficial or detrimental effect on rates of wound infection with suction groin wound drainage (RR, 0.96; 95% CI, 0.50 to 1.86) or from preoperative bathing with antiseptic agents compared with unmedicated bathing (RR, 0.97; 95% CI, 0.70 to 1.36).

Conclusions: There is clear evidence of the benefit of prophylactic broad-spectrum antibiotics for vascular reconstruction. Many other interventions intended to reduce the risk of infection in arterial reconstruction lack evidence of effectiveness.


Infection of biologic or prosthetic peripheral arterial grafts can lead to catastrophic outcomes ranging from loss of limb to death. The increasing prevalence of resistant bacteria has been associated with worsened outcomes. Many maneuvers are used in an attempt to reduce infection in arterial reconstructions, but there are no clear guidelines on the most appropriate or effective. Most graft infections are the result of the direct spread of bacteria from an infected wound; therefore, equal consideration needs to be given to the prevention and management of wound infection.

The aim of this systematic review and meta-analysis was to evaluate the evidence for the effectiveness of interventions to prevent wound and graft infection in peripheral arterial reconstruction and to identify areas where evidence is lacking.

METHODS

Randomized controlled trials (RCTs) evaluating any intervention undertaken with the intention of reducing or preventing infection in peripheral arterial surgery were identified by searches of The Cochrane Peripheral Vascular Diseases Group specialized register (last searched May 2006) and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (last searched Issue 2, 2006). The specialized register is constructed from electronic searches of United States National Library of Medicine database (MEDLINE; 1966 to date), Excerpta Medica database (EMBASE; 1980 to date), and Cumula-
RCTs that included patients undergoing peripheral arterial reconstruction with biologic or prosthetic graft were selected. Trials were excluded if they included patients with pre-existing graft infection or infection at the proposed operative site. Outcomes retrieved were wound or graft infection established by positive microbial cultures or clinical signs of infection. The Schulz et al 2 scale was used to assess quality of allocation concealment and the Jadad et al 2 scale to assess randomization method, blinding, and outcome of all study participants.

Statistical analysis. The statistical guidelines for review authors of the Cochrane Peripheral Vascular Diseases Group were used to analyze the data. Relative risk (RR) with 95% confidence intervals (CI) was used as a measure of effect for each dichotomous outcome. Where there were sufficient data, a summary statistic for each outcome was calculated by using a fixed-effect model and a random-effects model. Sensitivity analyses were undertaken to examine the stability of the results in relation to a number of factors, including study quality, the source of the data (published or unpublished), and patient type.

RESULTS

The search strategy identified 48 eligible reports, 35 of which are included in this review. Amongst these were 10 studies of antibiotic prophylaxis vs placebo, 6–12 3 studies of short-duration antibiotics (<24 hours) vs long-duration antibiotics (>24 hours), 6,13,14 5 studies of rifampicin impregnation of graft material, 15–18 2 studies of suction wound drainage, 19,20 and 3 studies of preoperative skin antisepsis. 21–23 A further 10 studies compared different prophylactic antibiotics or doses, 11,24–32 One trial each of intraoperative glove change, 33 wound closure technique, 34 and single dose vs antibiotics for 24 hours, 35 and two trials of a closed in situ bypass technique were also of adequate quality for inclusion. 36,37 One study was reported in two publications, 14,15 and one report 12 included 2 subgroups.

Infected outcomes in a subset of vascular patients could not be differentiated from the overall study population in one study of preoperative hair removal, 38 one study of a short vs a long course of cefamandole in vascular and thoracic patients, 39 and one study comparing cefazolin with ceftriaxone in cardiac and vascular patients. 40 These studies were therefore excluded, as were five studies where infective outcomes were not reported, 41–45 four quasi-randomized studies, 46–49 and one study with unclear inclusion criteria and equivalence of randomized groups. 50

All 35 included studies were RCTs. The methodologic quality of included studies varied greatly, with a mean Jadad score of 2.7 (range, 1 to 5). Quality was greatest for studies of prophylactic antibiotics where investigator and subject blinding were possible (Jadad mean, 3.1 [range, 2 to 5]; antibiotics vs placebo).

Reporting of allocation concealment was poor, with 22 studies failing to give a detailed description of randomization methods. Adequate methods of concealment were described in 11 of the 35 studies, and unconcealed randomization methods were used in two studies. 4,56

Prophylactic antibiotics versus placebo. Intravenous cefazolin was compared with placebo in three double-blind studies. Two of these included patients undergoing aortic and lower limb reconstructions using both prosthetic and vein grafts, 8,9 and one study included only patients undergoing vein grafting in the group randomized to placebo. 11 Intravenous cefuroxime in two dose regimens was compared with placebo in a single double-blinded study of lower limb prosthetic and vein bypasses, 6 and intravenous vancomycin was compared with placebo in a single unblinded study of prosthetic lower limb and aortic grafts. 7

Two unblinded studies randomized patients to intravenous cefazolin or placebo, 4,10 for lower limb arterial surgery. One of these studies 10 also included varicose vein operations, and there were two further randomization arms of topical cephradine wound instillation either alone or combined with intravenous cephradine. Results after arterial reconstruction could only be extracted for the subgroup of patients who received intravenous cephradine alone or placebo and who underwent arterial reconstruction with a prosthetic graft.

One unblinded study randomized patients undergoing procedures with prosthetic grafts to intravenous dicloxacillin or placebo. 5 A further double-blind study of patients undergoing aortic or lower limb reconstruction compared intravenous methylprednisolone plus netilmicin with placebo. 12 Tobramycin plus lincomycin were compared with placebo in a single study of prosthetic reconstructions. 9

Patients with pre-existing infection, wet gangrene, or who had received antibiotic therapy before surgery were excluded in six studies of antibiotic vs placebo. 6,8,10–12 Wound infection rates were recorded in all 10 studies, and early graft infection in all but two. 4,11

Studies of systemic antibiotics vs placebo showed a homogeneous pattern demonstrating a consistent benefit in reduction of wound infection in 1297 patients (RR fixed, 0.25; 95% CI, 0.17 to 0.38; P < .00001; Fig 1). Although no single study demonstrated a statistically significant reduction in early graft infection with prophylactic systemic antibiotics, the results of included studies appeared homogeneous, and in a fixed-effect model, a reduction in early graft infection was evident on meta-analysis (RR fixed, 0.31; 95% CI, 0.11 to 0.85; P = .02; Fig 2). Late graft infections were not identified in any study.

Four studies included patients undergoing aortic and lower limb surgery. One of these studies did not document the rates of infection for different surgical procedures. 7 The remaining three trials reported higher rates of infection 7,8,12 in aortic grafting compared with lower limb reconstruction. The RR of wound infection with prophylactic antibiotics was similar at 0.20 (95% CI, 0.08 to 0.48) for aortic and at 0.20 (95% CI, 0.06 to 0.69) for lower limb reconstructions.
Six of the 10 studies included patients with both prosthetic and vein grafts. Two reported differential infection rates.\textsuperscript{3,10} The RR was 0.51 (95% CI, 0.24 to 1.11) for wound infection with prosthetic grafts and 0.13 (95% CI, 0.04,0.41) for nonprosthetic grafts.

**Short-duration versus long-duration prophylactic antibiotics.** The three identified studies in which participants were randomized to prophylactic antibiotics for 24 hours and 5 days used different antibiotics and regimens. One study in lower limb reconstructions compared a 24-hour regimen of co-amoxiclav with a 5-day regimen; wound assessment was blinded.\textsuperscript{14} A further unblinded study randomized all patients undergoing open arterial surgery to intraoperative ticarcillin/clavulanate alone and intraoperative plus continued ticarcillin/clavulanate until all catheters were removed, but <5 days.\textsuperscript{13} The third study randomized participants to 24 hours of intravenous cefuroxime, 3 days of cefuroxime, or placebo. This double-blind study included only patients undergoing lower limb reconstruction and was the only study to exclude patients with pre-existing cellulitis, wet gangrene, or recent antibiotic therapy.\textsuperscript{15} Continuing prophylactic antibiotics for >24 hours did not appear to confer any additional benefit in reducing wound infection compared with a 24-hour regimen (RR fixed, 1.28; 95% CI, 0.82 to 1.98; Fig 3).

One study of a single dose of intravenous benzylpenicillin vs a 24-hour regimen was identified.\textsuperscript{35} This double-blinded study of general surgical patients included a vascular subgroup of 169 patients undergoing emergency or elective surgery through a midline abdominal incision. Wound infection rates were similar in both groups.

**Randomized controlled trials of different antibiotics or dose regimens.** Four studies of intravenous cefazolin randomized patients to receive cefazolin or cefamandole,\textsuperscript{27,30} cefuroxime,\textsuperscript{26} teicoplanin,\textsuperscript{31} or vancomycin.\textsuperscript{30} The prophylactic regimen varied from single 2-gram intravenous dose,\textsuperscript{31} to a 48-hour regimen of either 1 gram every 6 hours,\textsuperscript{30} or a 2-gram initial dose and subsequently 1 gram every 6 hours.\textsuperscript{26,27} One study compared a 48-hour regimen of 1 gram of cefazolin with a similar regimen of 2 grams of cefazolin.\textsuperscript{11}

Two studies randomized patients to intravenous cefuroxime, either as a single 1.5-gram dose compared with a single 2-gram dose of cephadolin,\textsuperscript{24} or a 24-hour regimen compared with 24 hours of oral ciprofloxacin.\textsuperscript{32}

Other randomized studies comparing antibiotics included single-dose 400-mg intravenous teicoplanin vs 24 hours of intravenous cephradine plus metronidazole,\textsuperscript{28} 2.2 grams of intravenous co-amoxiclav at induction and 4 hours vs 2 grams of cefoxitin at induction and 4 hours,\textsuperscript{25} and 0.75 grams cefamandole at induction, 4, and 10 hours vs 3 grams/200 mg ticarcillin plus clavulanic acid at induction, 4, and 10 hours.\textsuperscript{29}

There was no evidence of a significantly greater reduction in wound infection with comparable regimens of first-
generation or second-generation cephalosporins, penicillin/β-lactamase inhibitor, aminoglycosides, or the glycopeptides vancomycin or teicoplanin.

Rifampicin-bonded grafts. The results of three large studies of rifampicin bonding are reported in four articles.15-18 All trials used an identical method of rifampicin bonding, with soaking of a gelatin-coated Dacron graft in 1 mg/mL rifampicin for 15 minutes before insertion. The Joint Vascular Research Group trial15,18 included only patients undergoing extra-anatomic grafts (axillofemoral, femorofemoral and iliofemoral crossover grafts), whereas the Italian study16 included patients undergoing aorto-monofemoral, bifemoral, or iliofemoral grafts. Only patients with rifampicin allergy were excluded from either study, and both studies reported results up to 2 years.

All patients in the Joint Vascular Research Group study received three doses of an intravenous antibiotic as part of a local protocol,15 and 99% in the Italian study received intravenous cephalosporin.16 The European study included patients undergoing aorto-monofemoral grafts. This study’s wound and early graft infection results at 1 month were reported in a review article.17

The three multicenter studies of rifampicin bonding to gelatin-coated Dacron grafts reported early graft infection outcomes in 3379 patients. Two of these studies (857 patients) reported graft infection outcomes to 2 years. There was no evidence from these studies of a reduction in graft infection at 1 month (RR fixed, 0.63; 95% CI, 0.27 to 1.49; Fig 4) or 2 years (RR fixed, 1.05; 95% CI, 0.46 to 2.40; Fig 5).

Suction wound drainage. Two randomized studies of suction groin wound drainage were identified. One study randomized a single groin wound in patients undergoing arterial surgery through a longitudinal groin incision to suction drainage or no drainage.19 Identical dressings were applied after removal of the drains at 48 hours. Wound assessment thereafter was by a blinded assessor. The other study20 randomized right-side or left-side drainage in patients undergoing arterial surgery with bilateral groin inci-
sions. Drains were removed at the discretion of the surgeon, and wound assessment was unblinded.

There was no evidence that suction drainage of groin wounds conferred a beneficial or detrimental effect on rates of wound infection (RR fixed, 0.96; 95% CI, 0.50 to 1.86; Fig 6). The effect of suction wound drainage on early or late graft infection has not been studied.

Preoperative skin antisepsis. Preoperative antisepsis regimens using chlorhexidine were compared with placebo in two studies,21,22 and povidone iodine was compared with control in one further study.23 The chlorhexidine regimen involved painting all over with undiluted chlorhexidine and rinsing in the bath twice preoperatively21 or three preoperative showers with 4% chlorhexidine.22 The povidone iodine regimen consisted of twice-daily painting of skin from nipple to knees for 2 preoperative days.23 A preoperative bathing or shower regimen with antiseptic agents did not confer any benefit in reducing wound infection (RR, 0.97; 95% CI, 0.70 to 1.36; Fig 7). The effect on subsequent early or late graft infection has not been studied.

Other studies. Two studies of in situ lower limb bypass graft techniques reported wound infection outcomes. Both trials used methods to reduce the need for exposure of the entire vein bypass through a long incision in the leg. One study randomized patients to coil embolization of vein side branches or to a standard in situ technique.25 The other study compared angioscopically assisted valve lysis and vein branch identification that allowed minimal incisions with a standard technique that used an incision along the full length of the leg.26

Wound infection outcomes were measured in two studies of in situ lower limb bypass surgery in which techniques were used to minimize length of skin incisions. The outcomes of these two small studies differed: the trial of angioscopically assisted vein branch identification reported no effect on wound infection (RR fixed, 0.84; 95% CI, 0.06 to 12.86), and the trial of coil embolization of vein branches reported a significant reduction of wound infection complications (RR fixed, 0.47; 95% CI, 0.31 to 0.73). Wound observers in this latter trial were unblinded; therefore, the findings of this single study should be treated with some caution.

Single studies of intraoperative glove change33 and methods of wound closure34 failed to show any reduction in superficial wound infection.

DISCUSSION

Graft infection remains a serious limb-threatening and often life-threatening complication reported after 1% to 6% of all arterial reconstructions. Most deep wound and graft infections appear to be caused by implantation of bacteria from the patient’s skin at the time of surgery or by direct spread during the early postoperative period.51-53 Recently, resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) have increased in prevalence and now appear to account for most of the deep wound infections in the United Kingdom and Ireland.54 Measures to minimize the risk of infection are therefore essential in arterial reconstruction. Research on prevention of infection has mainly concentrated on antibiotic prophylaxis, with 22
of the 35 included articles studying the effects of systemic antibiotics. Many other interventions aimed at minimizing operative infection have been poorly studied.

In this review, the nonantibiotic interventions lacked evidence of effectiveness. The numbers of patients recruited to these studies were small, however, and this is reflected by the broader confidence intervals on meta-analyses.

**Preoperative measures.** Patients undergoing arterial reconstruction often have pre-existing risk factors for wound complications. Poor diabetes control, dependent limb edema, and poor nutrition may increase the risk of a significant wound and graft infection postoperatively. It seems sensible that these factors should be optimized before elective surgery, although we were unable to identify any trials of specific interventions for these risk factors. Increased bacterial colonization, particularly in groin creases, and colonization with resistant bacteria such as MRSA may also increase the risks of infection. This review found no evidence of any additional benefit with a more aggressive bathing or showering regimen that used antiseptics compared with simple bathing with nonmedicated soap. No trials of the effect of MRSA decolonization preoperatively were identified, despite evidence of efficacy in a systematic review in other specialties.55

**Operative and postoperative measures.** This review demonstrated that prophylactic treatment with systemic antibiotics commenced immediately preoperatively reduced the risk of wound infection and almost certainly early graft infection by between two thirds and three quarters. Broad-spectrum cephalosporins, penicillin/β-lactamase inhibitors, or aminoglycosides would appear to confer similar benefits. A high local prevalence of antibiotic-resistant organisms or pre-existing colonization with MRSA may necessitate use of vancomycin or teicoplanin. A 24-hour regimen of antibiotics appears as effective as prophylaxis continued >24 hours.

Basic theatre asepsis procedures are a prerequisite for arterial surgery. Evidence of the benefit of other theatre interventions is, however, very sparse. In particular, no RCTs of choice of skin antiseptic before surgery or use of bio-occlusive drapes were identified, and no trials of ultra-clean operating theater airflow for vascular surgery have been reported, although this is established practice for the insertion of orthopedic implants. Intraoperative glove change before handling prosthetic grafts did not seem to reduce contamination of graft material, and no effect on wound infection was detectable in the single small study.34

The use of rifampicin impregnation of prosthetic graft material appeared to have no benefit in preventing early or late graft infection. It has been speculated this may have been due to the low concentration of rifampicin used (1 mg/mL), and there remains scope for further research into the use of a vascular graft as a vehicle for drug delivery, particularly now that silver-coated grafts are available.56

The research analyzed here extended for almost 30 years. In the last decade, MRSA has changed the face of vascular infection. It is perhaps the most virulent organism currently challenging the vascular patient: aortic graft infection is almost universally fatal, and infrainguinal infection usually results in amputation. Few trials concerning MRSA infection exist in vascular surgery. The only investigations so far concern isolation policies that appear effective in open trials.57,58 This is an urgent problem in need of research focus.59

**CONCLUSION**

In addition to basic skin cleanliness and operating theater antisepsis procedures, patients undergoing arterial reconstruction should receive systemic antibacterial prophylaxis using an antibiotic with activity against staphylococcal and gram-negative bacteria. This review has exposed the limited nature of research in this area, despite the devastating effects of vascular graft infection. Large multicenter trials are needed, particularly with respect to the effects of bio-occlusive drapes and ultra-clean operating theater airflow.

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