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Abstract

Background: Vancomycin presoaking of the graft has been shown to decrease infection rates in some case series of anterior cruciate ligament (ACL) reconstruction. **Purpose:** We sought to substantiate the efficacy of vancomycin presoaked grafts for the prevention of infection after ACL reconstruction. **Methods:** We performed a systematic review of Medline and OVID to assess the incidence of postoperative infection in studies comparing patients undergoing ACL reconstruction with the use of vancomycin presoaked ACL grafts and a control group of patients undergoing ACL reconstruction without the use of presoaked grafts. The efficacy of vancomycin presoaking was calculated using the Agresti-Coull confidence interval. Relative risk (RR) was calculated for every study and the total sample. **Results:** The 11 studies that met inclusion criteria comprised 24,298 patients. In patients with vancomycin presoaking of the graft, 1 infection was reported in 8764 cases (0.01% rate). In the studies with control groups that did not have vancomycin presoaked grafts, there were 125 infections in 15,534 ACL reconstructions (0.8% rate). The efficacy of vancomycin presoaking in preventing infection after ACL reconstruction was 99.9% (0.999%–1.000% CI). The overall RR obtained was 0.07 (0.03–0.16 CI). All included studies were retrospective cohort studies (level III). **Conclusions:** Vancomycin presoaking of the graft has been shown to decrease infection rates after ACL reconstruction in studies of low evidence level. This suggests the need for prospective randomized controlled trials addressing this issue so that recommendations on the routine use of vancomycin presoaking of ACL grafts can be made with confidence.

Keywords

ACL reconstruction, infection, vancomycin, anterior cruciate ligament, prevention

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Introduction

Knee septic arthritis after anterior cruciate ligament (ACL) reconstruction is an uncommon but devastating complication [12,29]. Even with the best available treatment, it increases risk of long-term joint dysfunction due to graft failure and articular cartilage damage compared with an uneventful ACL reconstruction [9,15,17,18]. It has been theorized that a primary source of postoperative ACL reconstruction infection is graft contamination with skin commensal bacteria in both autograft and allograft scenarios [14]. How this happens remains unclear, with contamination after harvesting and preparation of the graft being the most accepted hypothesis when an autograft is used [21].

The standard of care for preventing infection in orthopedic surgery is the use of intravenous (IV) prophylactic antibiotics [5]. A recent systematic review [6] found a 2-fold infection rate in patients not receiving IV antibiotics before knee arthroscopy. Notably, the search did not yield

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any publications related to ACL reconstruction that did not use antibiotic IV prophylaxis. Despite its use, the reported incidence of infection in ACL reconstruction ranges from 0.14% to 1.7% [12].

Vertullo et al in 2012 [28] described the vancomycin presoaking technique. The practice involves wrapping the prepared graft with a gauze swab previously saturated in a 5 mg/mL vancomycin solution while the arthroscopic part of the surgery is performed. The rationale for the use of vancomycin is based on its pharmacokinetic properties [11] including low allergenicity, heat stability, safety for local use, and large volume of distribution. It has a bactericidal action against skin commensals, which are the most common pathogens isolated in ACL reconstruction infection by far [29].

Vertullo et al [28] showed initial success in decreasing the infection rate after ACL reconstruction using hamstring autografts. In 2019, Naendrup et al [19] published a systematic review and meta-analysis on the early reports of this technique, including some unpublished material. After this research was published, an important number of articles using the same protocol have appeared, including a larger variety of grafts and concomitant procedures.

We aimed to systematically review the literature to analyze data that compare the use of vancomycin presoaking as prevention for infection in ACL reconstruction to control groups of patients who did not undergo vancomycin presoaking. It is hypothesized that vancomycin presoaking is an effective infection prevention method in ACL reconstruction, regardless of the type of graft or concomitant procedures.

Methods

We searched the literature for studies, written in English, that (1) compared the use of vancomycin presoaked grafts with a control group (no vancomycin presoaked grafts) in patients undergoing ACL reconstruction and (2) assessed whether there were any differences in the infection rate in ACL-reconstructed patients with or without the use of vancomycin presoaking of the graft. Previous systematic reviews or narrative reviews were excluded.

Two databases (MEDLINE and Ovid) were searched per PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines on December 1, 2020. The terms “(anterior cruciate ligament OR ACL) AND ((OR prevention) AND vancomycin)” were used. The PRISMA statement was used for reporting study selection.

Full text was obtained for all studies matching inclusion criteria. These were reviewed to reconfirm eligibility. The authors performed study selection independently. Disagreement was resolved by consensus.

Collection of all relevant information regarding the study design, population, intervention group, control group,

outcomes, methodological quality, and duration of follow-up was performed. The methodological quality of each eligible study was graded using the MINORS (Methodological Index for Non-randomized Studies) [27] checklist.

Data were extracted from the included studies and recorded in a Microsoft Excel spreadsheet (Redmond, WA). The recorded data included study characteristics as well as type of graft used, type of surgery and concomitant procedures, clinical outcomes, and the use of vancomycin presoaked grafts. These data were summarized descriptively.

The efficacy of vancomycin presoaking was calculated performing an analysis of the data using Agresti-Coull confidence interval (CI). Relative risk (RR) was calculated individually for every study; in addition, the overall RR was calculated. Heterogeneity was calculated using the χ^2 and Higgins's tests. Statistical significance was set at $P < 0.05$.

Statistical analysis was performed using the STATA 16 Software (StataCorp LLC, College Station, TX).

Results

A total of 160 studies were found, and the full text was reviewed for 26 articles. Eleven articles published between 2012 and 2020 with a total of 24,298 patients (8764 ACL reconstructions with vancomycin presoaked grafts and 15,534 ACL reconstructions without vancomycin presoaked grafts) were considered eligible (Fig. 1). The 11 studies included reached a score of 16/24 for comparative studies in the MINORS checklist [27]. The general characteristics of the studies reviewed are summarized in Table 1. The data regarding infection after ACL reconstructions with and without vancomycin presoaked grafts are summarized in Table 2.

All the studies included in this systematic review were level III studies [2–4,8,20,22–25,28,30]. Two studies reported on the same patient population, with the follow-up study including a larger number of patients in the treatment group (vancomycin) and the same control group of the former study [23,28]. The duplicated group of patients was excluded from the meta-analysis. Patient demographics were reported in 8 of the included studies. Regarding graft type inclusion, 4 studies included only hamstring autografts [8,23,28,30], while the rest of the studies included hamstrings as the main graft as well as patellar tendon, quadriceps tendon, tensor fasciae latae, or allograft. Nine studies specified the amount of each graft utilized in percentages or in exact numbers. Unfortunately, regarding infection, only 5 studies (4 m using only hamstring grafts) [2,8,23,28,30] reported the type of graft in infected patients, preventing the possibility of analyzing data on graft type differences. Three studies [3,4,28] included open procedures (collateral ligament repair/reconstructions or extra-articular tenodesis) in the same surgical act as the ACL reconstruction.

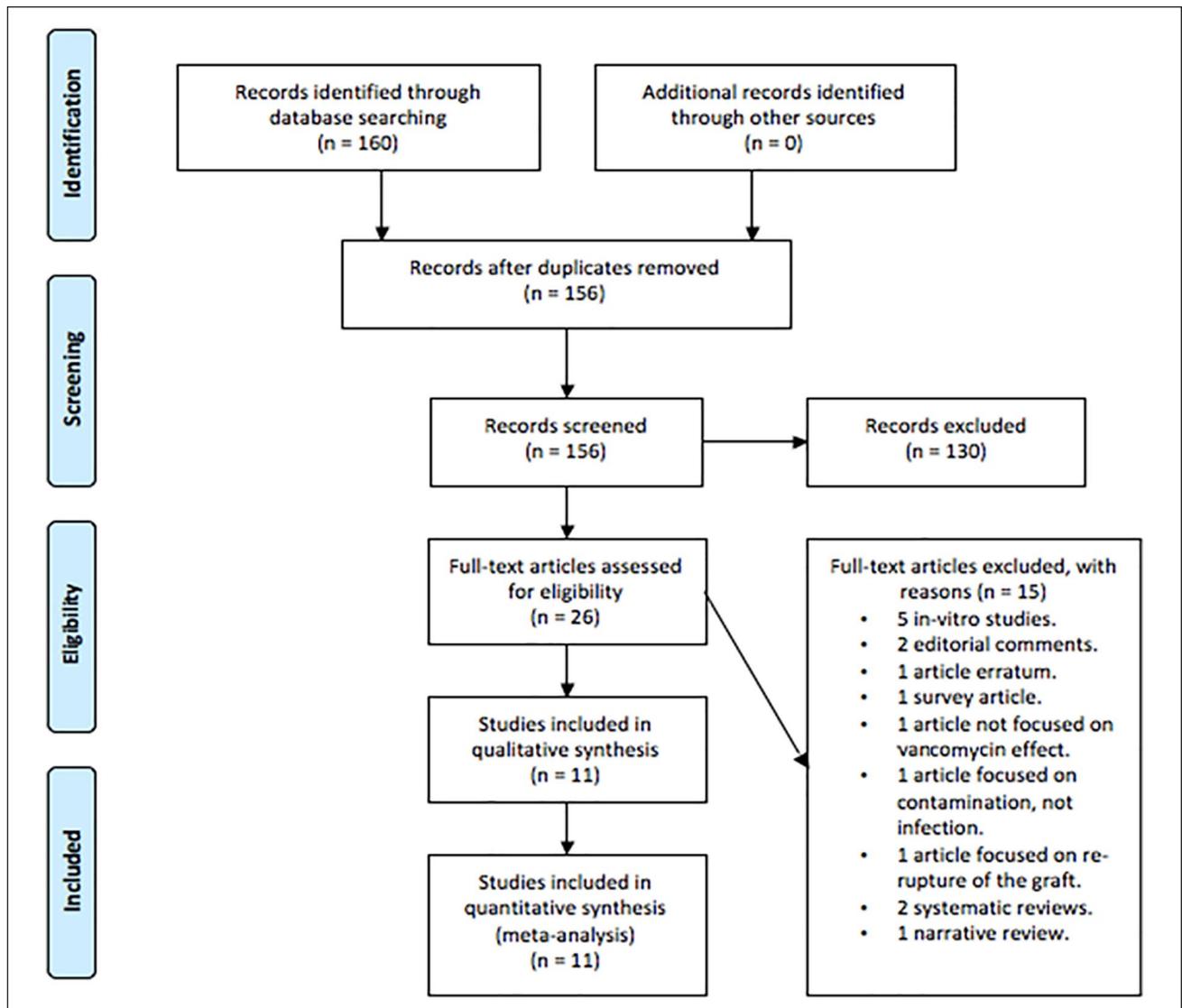


Fig. 1. The preferred reporting items for systematic reviews and meta-analyses flowchart describing the selection process for included and excluded articles.

All studies used a first- or second-generation cephalosporin as routine preoperative IV prophylaxis with optional antibiotics for allergic patients. Vancomycin presoaking was done using a solution with a concentration of 5 mg/mL of vancomycin, as described by Grayson et al [11] in all studies, except for a study that used a 1 mg/mL vancomycin concentration [3]. Ten of the studies used a soaked gauze swab to deliver vancomycin to the graft; the majority of these studies also soaked the graft directly in the solution before covering the graft with the gauze swab. One study soaked the graft directly in the solution as the only method to deliver vancomycin [4]. Eight studies reported the duration of graft soaking (10 to 20 minutes).

In all studies, the incidence of postoperative septic arthritis was assessed by the operating surgeon in follow-up

appointments. However, the definition of septic arthritis and the follow-up protocol varied among the studies, with only 2 studies [8,20] reporting objective synovial fluid values for defining septic arthritis; 2 studies [4,24] did not report any diagnostic criteria for septic arthritis. Follow-up ranged from 1.5 months to 37 months. One study did not report follow-up [22].

Regarding the effect of vancomycin presoaking on the incidence of septic arthritis after ACL reconstruction, 10 of the 11 studies showed statistically significant differences favoring vancomycin as an effective strategy, with only 1 study [4] that did not show a statistically significant *P* value. Only 1 case of septic arthritis after vancomycin use was reported [3]; the rest of the studies reporting no cases of septic arthritis after the use of vancomycin presoaking. The

Table 1. Characteristics of included studies.

Study (year of publication)	Level of evidence	Minimum follow-up (months)	Mean age in vancomycin group (years)	Mean age in non-vancomycin group (years)	Number of patients in vancomycin group	Number of patients in non-vancomycin group
Vertullo et al [28]	III	12 months	30	30	870	285
Perez-Prieto et al [22]	III	Not reported	Not reported	Not reported	734	810
Phegan et al [23]	III	12 months	29	30	1300 (430 new)	285 (0 new)
Offerhaus et al [20]	III	37 months	31	32	853	926
Figuroa et al [8]	III	5 months	Not reported (mean age of all sample 29)	Not reported (mean age of all sample 29)	260	230
Baron et al [3]	III	3 months	28	28	798	842
Schuster [24]	III	1.5 months	Not reported	Not reported	503	1577
Bohu et al [4]	III	12 months	30	30	490	1184
Schuster [25]	III	1.5 months	Not reported	Not reported	2243	7968
Banios et al [2]	III	6 months	30	29	593	1242
Wan et al [30]	III	9 months	26	27	120	185

Table 2. Data regarding infection after anterior cruciate ligament reconstructions with and without Vancomycin presoaked grafts.

Study (year of publication)	Infected patients with vancomycin presoaked grafts/total patients (%)	Infected patients with non-vancomycin presoaked grafts/total patients (%)	P value
Vertullo et al [28]	0/870 (0)	4/285 (1.4)	.016
Perez-Prieto et al [22]	0/734 (0)	15/810 (1.9)	<.001
Phegan et al [23]	0/1300 (0)	4/285 (1.4)	.0011
Offerhaus et al [20]	0/853 (0)	22/926 (2)	.001
Figuroa et al [8]	0/260 (0)	4/230 (1.7)	<.05
Baron et al [3]	1/798 (0.1)	10/842 (1.2)	.032
Schuster [24]	0/503 (0)	14/1577 (0.9)	.029
Bohu et al [4]	0/490 (0)	7/1184 (0.6)	.08
Schuster [25]	0/2243 (0)	35/7968(0.4)	.001
Banios et al [2]	0/593 (0)	7/1242 (0.6)	.031
Wan et al [30]	0/120 (0)	3/185 (1.6)	<.01

single infection case was the only case in 8764 patients (from the 11 studies), independent of graft type or the presence of concomitant ligament procedures or open surgeries, for a 0.01% total infection rate. The control groups of the studies reviewed, including 15,534 ACL reconstructions without vancomycin presoaking, presented 125 infections, accounting for a 0.8% infection rate.

Vancomycin presoaking after ACL reconstruction had an estimated efficacy in preventing infection of 99.9% (0.999%–1.000% CI) using the Agresti-Coull CI. The overall RR obtained was 0.07 (0.03–0.16 CI), meaning that vancomycin presoaking provided a 93% risk reduction compared with control patients (Fig. 2).

Discussion

In this systematic review of available studies (all level III), vancomycin presoaking of the graft showed a decrease in

infection rates after ACL reconstruction, with only 1 infection reported in 8764 patients, independently of the graft type used or the presence of concomitant ligament procedures or open surgeries. In the studies reviewed, 15,534 ACL reconstructions performed without vancomycin presoaked grafts resulted in 125 infections, accounting for a 0.8% infection rate. Baron et al [3] reported the only case of infection after vancomycin presoaking of a graft, but the type of graft, type of surgery, and concomitant procedures of that case were not reported.

One of the limitations of the studies reviewed is that all are level III comparative studies, with no prospective randomized trials. Further investigations with a higher level of evidence and designs involving subgroup analyses will be of high interest to obtain data on which patients are the best candidates to receive this prophylaxis. Another limitation is that the studies were heterogeneous in their methods of vancomycin presoaking, the duration of presoaking, follow-up,

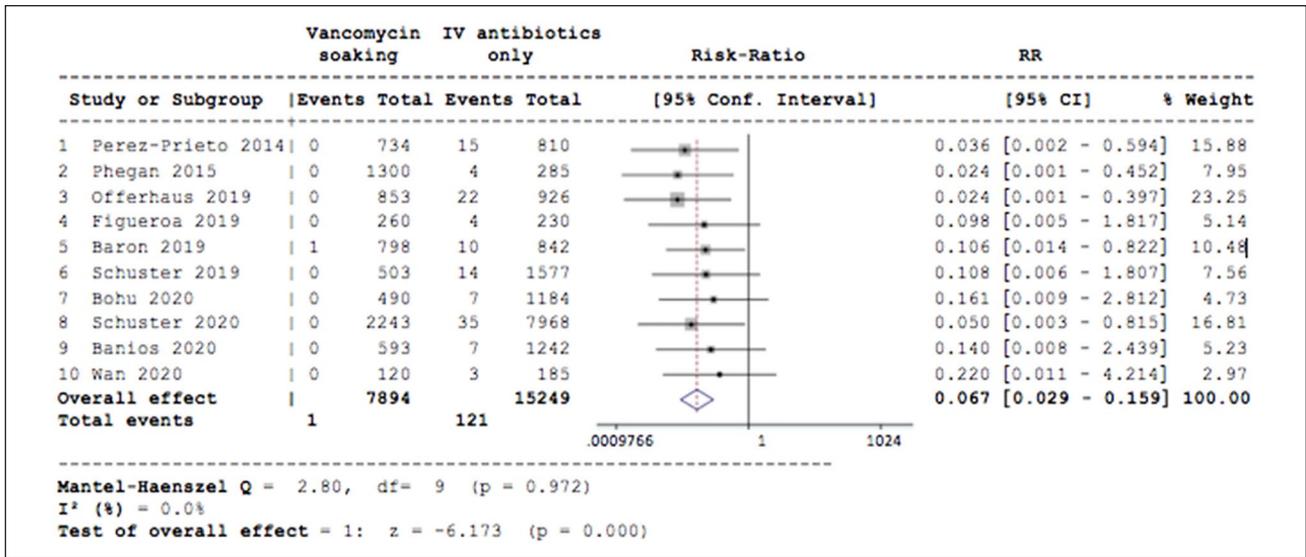


Fig. 2. A forest plot with individual and overall relative risk in patients following anterior cruciate ligament reconstruction with and without vancomycin presoaked grafts. *CI* confidence interval.

presence of additional open procedures, and diagnosis of septic arthritis, among other factors. Inclusion and exclusion criteria of these studies were often insufficiently reported.

One of the main questions on vancomycin use is the time of presoaking needed to obtain the desired effect. Grayson et al [11], in a controlled laboratory study considered to be the basis of the clinical studies that followed, reported that tendon grafts wrapped in impregnated gauze swabs and left to stand for 10 minutes allowed a sufficient release of vancomycin from the soaked tendon grafts to create a minimum inhibitory concentration for *Staphylococcus*. Unfortunately, graft-soaking time was not homogeneous among the studies we reviewed. Schüttler et al [26] in a controlled laboratory study suggested that when using the concentration described by Vertullo et al [28] (5 mg/mL), 20 minutes of vancomycin presoaking was needed to clean the 100% of tendons studied, a timeframe that was not accomplished by any of the studies reporting presoaking time. On the other hand, most of the studies followed the same guidelines for vancomycin concentration (5 mg/mL), but 1 study [3] (presenting the only infection case) reported a reduced concentration of solution (1 mg/mL). Future studies should have stricter methodologies to be able to recommend the minimum time of presoaking and concentrations needed to obtain adequate infection prevention.

There is also data showing that the technique is not widely used. Ekdahl et al [7], in a recently published study, surveyed Swedish surgeons registered in the Swedish Knee Ligament Register and noted that only 8% of them, accounting for 13% of surgeries, used vancomycin-soaked grafts. Prolonged IV antibiotic prophylaxis was used more often

than vancomycin presoaking, with 3% of the respondents using it in every case and 38% using a risk-based assessment for decision making. Despite the positive outcomes of vancomycin presoaking in the presented studies, prophylactic IV antibiotic administration is still the standard of care [5] and its replacement for vancomycin presoaking is not recommended. Vancomycin presoaking used in conjunction with IV antibiotic prophylaxis is the preferred option.

Another concern with the use of vancomycin-soaked grafts is the unknown immediate and long-term effects of vancomycin on graft properties. Regarding the biomechanical security of the use of vancomycin at time zero, Schüttler et al [26] published a porcine model of tendons soaked with sterile compresses under different concentrations of vancomycin for either 10 or 20 minutes, starting with 1 mg/mL and increasing to 2.5, 5, and 10 mg/mL. Tendons were tested for maximum load and elongation during testing. After soaking, the tendons showed no signs of biomechanical impairment. Similarly, Jacquet et al [13] in a study using living donors found that presoaking of human semitendinosus grafts with vancomycin (5 mg/mL) in a solution does not alter their biomechanical properties at time zero compared with a control group presoaked in saline solution.

Although there are no controlled studies regarding long-term biomechanical effects of its use, Offerhaus et al [20] found a significant decrease of graft failure in patients with vancomycin presoaked grafts and no increase in the rate of postoperative arthrofibrosis and subjective outcome scores compared with a control group without vancomycin. Similarly, Bohu et al [4] found no differences in return to running and overall knee function when compared with

control patients. In addition, they found that more patients with vancomycin presoaked grafts returned to their preinjury sport compared with their control counterparts.

There is also apprehension that the use of vancomycin could change the growth of the bacterial community at surgical sites, leading to the growth of uncommon bacterial communities, especially gram-negative bacteria and resistant microorganisms [1,10]. A recent meta-analysis in spinal surgery [16] demonstrated that the topical administration of vancomycin did not increase the rates of gram-negative bacterial or polymicrobial infections in surgical sites, although there are no reports to date on this potential complication in knee arthroscopy.

The level III evidence available demonstrates a decrease in the infection rate after ACL reconstruction with vancomycin presoaking of the graft (independently of the graft type used or the presence of concomitant ligament procedures or open surgeries). Short-term effects related to vancomycin presoaking do not appear to adversely affect graft performance. The available evidence suggests that there is no long-term compromise of graft performance, with clinical results being comparable to patients in which no vancomycin is used. The lack of controlled, prospective, randomized trials makes it difficult to recommend vancomycin presoaking of the graft universally for ACL reconstruction. Level I, randomized, well-controlled trials are needed to provide stronger evidence on which to base recommendations for practice.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: David Figueroa reports a relationship with Stryker, outside the submitted work. Rafael Calvo reports a relationship with Stryker, outside the submitted work. Alex Vaisman reports a relationship with Arthrex, outside the submitted work. The other authors declared no potential conflicts of interest.

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Human/Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent

Informed consent was waived from all patients included in this study.

Level of Evidence

Level III: Systematic review of level III studies.

Required Author Forms

Disclosure forms provided by the authors are available with the online version of this article as supplemental material.

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