



# Vancomycin presoaking of hamstring autografts to prevent infection in anterior cruciate ligament reconstruction: a narrative review

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- Hamstring autograft use has been linked to an increased risk of infection after anterior cruciate (ACL) reconstruction compared to other grafts. The absolute reason for this remains unclear, with contamination after harvesting and preparation of the graft being the most accepted hypothesis.
- Using the rationale that a contaminated graft could be the main factor in postoperative septic arthritis and in an effort to maximize the antibiotic efficacy of the graft, the Vancomycin presoaking technique was developed. It has shown success in decreasing the infection rate in ACL reconstruction. In recent years, an important number of research articles using this protocol have appeared, but the technique is still not widely implemented.
- Recent literature shows that Vancomycin presoaking of the graft has shown a successful decrease in the infection rate after hamstring autograft ACL reconstruction. It has also shown efficacy decreasing the infection rate in other types of grafts (patellar tendon, quadriceps tendon, allograft) and also in patients with concomitant ligament procedures or open surgeries.
- Despite the positive effects of Vancomycin presoaking reducing the infection rate after ACL reconstruction, the lack of prospective randomized control trials and the heterogeneity of the different studies mean it is not feasible to recommend Vancomycin presoaking of the graft universally for every ACL reconstruction patient.

**Keywords:** ACL; infection; Vancomycin

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## Introduction

Knee septic arthritis after anterior cruciate ligament (ACL) reconstruction is an uncommon but devastating complication, with a reported incidence of 0.14% to 1.7% on the literature.<sup>1,2</sup> Even providing state of the art treatment, there is an increased risk of articular cartilage damage and graft failure and a long-term risk of joint dysfunction.<sup>3-6</sup> Hamstring autograft use has been linked to an increased risk of infection after ACL reconstruction compared to other grafts such as patellar tendon, quadriceps tendon, or allograft.<sup>7,8</sup> The absolute reason for this remains unclear, with contamination after harvesting and preparation of the graft being the most accepted hypothesis.<sup>9</sup>

Using the rationale that a contaminated graft could be the main factor in postoperative septic arthritis and in an effort to maximize the antibiotic efficacy on the graft, Vertullo et al in 2012<sup>10</sup> described the Vancomycin presoaking technique. The practice involves wrapping the already prepared graft with a swab previously saturated in a 5 mg/mL Vancomycin solution while the surgeon performs the arthroscopic part of the surgery. The rationale for the use of Vancomycin is down to its pharmacokinetic properties that make it an ideal agent.<sup>11</sup> These include low allergenicity, heat stability, safety for local use, and large volume of distribution. It has a bactericidal action against skin commensals such as *Staphylococcus Aureus* and *Coagulase Negative Staphylococci*, which are the most common pathogens isolated in ACL reconstruction infection by far.<sup>2</sup>

The Vertullo et al<sup>10</sup> study showed success in decreasing the infection rate in ACL reconstruction when using Vancomycin. In the following years, an increasing number of research articles using the same protocol have been

published. Nevertheless, the technique is still not widely implemented. Recently, a survey on Swedish surgeons<sup>12</sup> noted that only an 8% of them used Vancomycin-soaked grafts and that the use of Vancomycin accounted for 13% of all ACL surgeries.

The aim of this narrative review is to present the available evidence and the different experiences using the Vancomycin presoaking technique to decrease infection after ACL reconstruction, emphasizing its use in hamstring autograft, considering that it has an increased risk of infection compared to other grafts.

### Available studies

Vertullo et al<sup>10</sup> in the first published study on the topic retrospectively analysed data on 1,135 consecutive patients who underwent ACL reconstruction during a seven-year period. In the initial three-year period, 285 patients underwent ACL reconstruction with a hamstring autograft with preoperative intravenous (IV) antibiotics. In the subsequent four-year period, 870 patients underwent ACL reconstruction with a Vancomycin presoaked hamstring autograft with preoperative IV antibiotics. Patients who required simultaneous meniscal repair or posterolateral repair or reconstruction were included in the study. In the first period, a total of four postoperative joint infections were documented (1.4%) while no infections were documented for Vancomycin presoaked hamstring grafts. Known failures were similar in each group. Three years later, the same group<sup>13</sup> published a follow-up study increasing the number of patients using Vancomycin presoaked hamstring autografts to 1,300 individuals, reporting no postoperative infections (0%).

Pérez-Prieto et al in 2014<sup>14</sup> published a retrospective analysis of all ACL reconstructions over an eight-year period in two university hospitals. In the initial four-year period, all patients were operated under classical antibiotic IV prophylaxis. Over the last four-year period, this prophylaxis was supplemented with Vancomycin presoaking of the autograft. There were 810 patients with only antibiotic IV prophylaxis and 734 patients for whom Vancomycin presoaking of the graft was added. Fifteen cases of knee joint infections were identified in the series (0.97%). All of these infections occurred in patients with no Vancomycin presoaking of the graft, representing a rate of infection of 1.85% in comparison with 0%. Unlike the previous series, this study included patellar tendon autografts in a small proportion (16%).

After a paucity of four years without studies on the topic, Offerhaus et al<sup>15</sup> published a study focusing not only on the effect of Vancomycin presoaked grafts in postoperative infection, but also assessing for complications, including graft failure or arthrofibrosis. They carried out a retrospective review of 1,779 patients who underwent

ACL reconstruction over a period of five years, analysing the rate of postoperative deep knee infection. Different types of autografts and revision ACL surgery in unknown numbers (not reported in the study) were included. To analyse possible side effects associated with Vancomycin use, 500 patients out of the overall study population were randomly selected and retrospectively interviewed for further postoperative complications including graft failure and arthrofibrosis as well as subjective evaluation of their knees by completing the International Knee Documentation Committee (IKDC) form with a minimum mean follow-up of 37 months. For these last outcomes, they excluded from analysis any graft different from hamstring, as well as revision ACL surgery. Twenty-two out of 926 patients (2%) without Vancomycin presoaked grafts suffered a postoperative deep knee infection. In contrast, there were no postoperative infections in 853 patients where Vancomycin presoaked grafts were used (0%). Analysis of the random sample revealed a significant decrease of graft failure with eight re-ruptures in 257 patients (3%) in the Vancomycin group compared to 16 cases of graft failure in 167 patients (10%) in the control group. No differences were found in the rate of postoperative arthrofibrosis, Tegner or subjective outcome scores.

During the same year, Figueroa et al<sup>16</sup> published their experience on 260 patients with Vancomycin presoaked hamstring autografts versus 230 patients with the same graft but without using Vancomycin. They reported four cases of septic arthritis without Vancomycin (1.7%), while no cases of septic arthritis were noted in the Vancomycin patients during the study period.

Baron et al,<sup>17</sup> in a study on 1,640 cases (798 using Vancomycin presoaked grafts), reported the first known infection in ACL surgery after the use of Vancomycin presoaking. Unlike the previous studies, this one in particular included a significant number of allograft use (27.2%), and also smaller numbers of hybrid grafts (4.7%), revision ACL surgery (15.9%) and other ligament procedures (9.2%). The text does not make a clear differentiation on the type of autograft used, but it states that hamstring autograft was used in a 46.5% of the cases. Regarding the infection case reported, it accounts for 0.1% of the whole Vancomycin presoaked graft cohort versus a 1.2% rate of infection in the group without Vancomycin. Unfortunately, the Vancomycin infection case and its specific demographic and surgical variants were not described.

Schuster et al<sup>18</sup> published a study addressing specifically only revision ACL surgery with and without soaking of the graft in Vancomycin solution. Five hundred and seventeen patients with Vancomycin presoaked grafts were compared to 1,638 patients with no Vancomycin added. Hamstring autografts were used in 1,310 patients (60.8%) and quadriceps tendon autografts were used in 845 patients (39.2%). There were 14 cases of postoperative

**Table 1.** Summary of hamstring autografts presoaked in Vancomycin in different studies and number of infected grafts

Study (year of publication)	Level of evidence	Study design	Minimum follow-up (months)	Number of Vancomycin presoaked hamstring autografts	Number of infected grafts
Vertullo (2012) <sup>10</sup>	III	Retrospective	12 months	870	0
Perez-Prieto (2014) <sup>14</sup>	III	Retrospective	Not reported	Not reported	0
Phegan (2015) <sup>13</sup>	III	Retrospective	12 months	430 new cases (1,300 total cases)	0
Offerhaus (2019) <sup>15</sup>	III	Retrospective	37 months	Not reported	0
Figueroa (2019) <sup>16</sup>	III	Retrospective	5 months	260	0
Baron (2019) <sup>17</sup>	III	Retrospective	3 months	Not reported	0 or 1 (graft type not reported)
Schuster (2019) <sup>18</sup>	III	Control group: retrospective Treatment group: prospective	1.5 months	306	0
Bohu (2020) <sup>20</sup>	III	Retrospective	12 months	352	0
Schuster (2020) <sup>19</sup>	III	Control group: retrospective Treatment group: prospective	1.5 months	2,277	0
Banios (2020) <sup>21</sup>	III	Retrospective	6 months	415	0
<b>Total</b>				<b>4,910</b>	<b>0 or 1</b>

septic arthritis in grafts without Vancomycin (0.9%), and none in Vancomycin presoaked grafts (0%). The same group published a few months later their experience with the same protocol in primary ACL reconstructions.<sup>19</sup> Hamstring autograft was used in 99% and quadriceps autograft was used in 1% of the cases. There were 35 cases of postoperative septic arthritis without Vancomycin (0.4%), and none in Vancomycin presoaked grafts (0%).

Bohu et al<sup>20</sup> conducted a study to compare return to sports and knee function one year after ACL reconstruction using autografts with and without Vancomycin presoaking. In this series, 79.3% of the patients were operated using a hamstring autograft. Interestingly, 40.6% of the cohort had an extra-articular tenodesis procedure. Regarding infection, seven patients presented this complication in the group without Vancomycin, while this was not found in patients with Vancomycin presoaked grafts. No significant difference was identified in the return to running between the two groups one year after surgery. Significantly more patients with Vancomycin presoaked grafts returned to their pre-injury sports and overall knee function was comparable between the groups.

Finally, Banios et al<sup>21</sup> in the latest study published on the topic compared 593 patients with Vancomycin presoaked autografts to 1,242 autografts without the use of Vancomycin. Patellar tendon autograft was used in 26.6% of the patients, and hamstring autograft was used in 76.4% of the cohort. Postoperative septic arthritis occurred in seven patients without Vancomycin (0.56%). All infected cases had a hamstring autograft implanted. There were no postoperative infections (0%) in the Vancomycin group.

All the studies regarding Vancomycin presoaking of the graft in ACL reconstruction are level III studies, with a paucity of prospective randomized research. A summary of the number of Vancomycin presoaked grafts and rates of infection of the different studies is displayed in Table 1. Those that used Vancomycin had an infection rate of 0%.

## Discussion

Vancomycin presoaking of the graft has shown a successful decrease in the infection rate after hamstring autograft ACL reconstruction in the different studies reviewed. It has also shown efficacy decreasing the infection rate in other types of grafts (patellar tendon, quadriceps tendon, allograft) and also in patients with concomitant ligament procedures or open surgeries (lateral extra-articular tenodesis, posterolateral corner repair/reconstruction, among others). Table 1 summarizes the total number of hamstring autografts presoaked in a Vancomycin solution extracted from the different studies reviewed, which reaches 4,910 hamstring autografts with no infections (0%). There are three studies (Pérez-Prieto et al,<sup>14</sup> Offerhaus et al<sup>15</sup> and Baron et al<sup>17</sup>) that did not report the exact number of hamstring autografts that were presoaked, but in most of them it is clearly understood that hamstring grafts were the major number of grafts used. Baron et al<sup>17</sup> reported the only case of infection after Vancomycin presoaking of a graft, but unfortunately, the type of graft and demographic data of that case (type of surgery, concomitant procedures, open or arthroscopic surgery) were not reported.

One of the limitations of the studies reviewed is that all of them are case control studies (level III evidence), with a paucity of prospective randomized research. Further investigations with a higher level of evidence, and designs involving subgroup analyses would be of high interest to obtain data on which patients would be the best candidates to receive the prophylaxis.

An important concern with respect to Vancomycin use is the time of presoaking required to obtain the effect desired. In Grayson et al's<sup>11</sup> laboratory study, which is considered the basis of the clinical studies that followed, tendon grafts were wrapped in impregnated gauze swabs and left to stand for 10 minutes. This allowed a sufficient

release of Vancomycin from the soaked tendon grafts to create a minimum inhibitory concentration for *Staphylococcus*. Unfortunately, most clinical studies have presented a broad range of presoaking time. In Schuster et al's<sup>19</sup> article, the soaking time between preparation and implantation was  $13 \pm 6$  minutes with a range from 1 to 41 minutes. Figueroa et al<sup>16</sup> kept every graft wrapped for at least 15 minutes while the arthroscopic stage of the reconstruction was performed. Schüttler et al,<sup>22</sup> in a controlled laboratory study, suggested that when using the concentration described in Vertullo et al's<sup>10</sup> study (5 mg/ml), 20 minutes of Vancomycin presoaking were needed to clean the 100% of tendons studied. Similarly, the Vancomycin delivery method has not been standardized between studies. Nine of the articles used a soaked gauze swab as the method to deliver Vancomycin to the graft, with the majority of these studies also soaking 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. Regarding rinsing the soaked tendons, Grayson et al<sup>11</sup> recommended caution, because this decreases the concentration of Vancomycin release from the graft; however, some studies did rinse the grafts with saline before implantation. Future studies should have stricter methodologies to be able to make a recommendation on an evidence-based Vancomycin delivery technique to obtain adequate infection prevention. Given the heterogeneity of the methodology of the different studies, it is impossible to state that all soaking methods reach the minimum inhibitory concentration for common bacteria involved in ACL infections.

There are also data showing that the technique is not widely used. Ekdahl et al,<sup>12</sup> in a recently published study, carried out a survey of Swedish surgeons who are 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 at a higher rate than Vancomycin presoaking, with 3% of the respondents using it in every case and 38% using a risk-based assessment to make a decision. Despite the positive outcomes of Vancomycin presoaking in the presented studies, prophylactic IV antibiotics are still the standard of care<sup>23</sup> and their replacement by Vancomycin presoaking is not recommended (Vancomycin presoaking should be used in conjunction with IV antibiotic prophylaxis).

Another source of concern in the use of Vancomycin in grafts is related to the unknown immediate and long-term effects of this technique. Regarding the biomechanical security of the use of Vancomycin at time zero, Schüttler et al<sup>22</sup> published a porcine tendon model that showed no signs of biomechanical impairment of porcine flexor tendons after the use of Vancomycin wraps with concentration ranging from 1 to 10 mg/ml for 10 or 20 minutes at

time zero testing. Similarly, Jacquet et al<sup>24</sup> in a study using living donors found that presoaking of human semitendinosus grafts with vancomycin (5 mg/mL) does not alter their biomechanical properties at time zero. Until now, there have been no studies regarding long-term biomechanical effects of its use, however, Offerhaus et al<sup>15</sup> published 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 to a control group without Vancomycin, and Bohu et al<sup>20</sup> found no differences in return to running and overall knee function with control patients. In addition, they found that more patients with Vancomycin presoaked grafts returned to their pre-injury sport compared to their control counterparts.

Another important concern are the legal implications involved in this off-label clinical use of Vancomycin. The World Health Organization guideline accepts off-label prescription as legal if it follows ethical guidelines and safety regulations.<sup>25</sup> In some countries, prescribing off-label medications is legally accepted by a registered prescriber, however, healthcare professionals may have more responsibility in prescribing off-label than on-label medications.<sup>26,27</sup> These legal implications could prevent surgeons from using Vancomycin presoaked grafts, and therefore local regulations should be reviewed before initiating its use.

There is also apprehension that the use of Vancomycin will change the growth of the bacterial community at surgical sites, leading to the growth of uncommon bacterial communities, especially in gram-negative bacteria and microorganisms,<sup>28,29</sup> however, a recent meta-analysis in spinal surgery<sup>30</sup> demonstrated that the topical administration of Vancomycin did not increase the rates of gram-negative bacterial or polymicrobial infections in surgical sites. Chondrocyte viability in a Vancomycin environment has also been named as a potential complication of this technique, with studies suggesting that a concentration higher than 5 mg/mL might be detrimental for articular cartilage.<sup>31</sup> Nevertheless, Grayson et al<sup>11</sup> demonstrated that Vancomycin concentrations released from tendons are much lower than the levels needed to harm chondrocytes. Also, case reports<sup>32</sup> have been published about possible systemic side effects of the use of topical Vancomycin, but without any publications related to arthroscopic knee surgery yet.

Despite the positive effects of Vancomycin presoaking reducing the infection rate after ACL reconstruction shown in the different studies reviewed, the lack of prospective randomized control trials and the heterogeneity of the different studies means it is not feasible to recommend Vancomycin presoaking of the graft universally for every ACL reconstruction patient. Considering this information, the authors recommend presoaking grafts in

Vancomycin for patients with known risk factors for infection. Especially when using hamstring autograft because it has been linked to an increased risk of infection after ACL reconstruction compared to other grafts.<sup>7,8</sup>

## Conclusion

Hamstring autograft use has been linked to an increased risk of infection after ACL reconstruction compared to other grafts. Vancomycin presoaking of the graft has shown a successful decrease in the infection rate after hamstring autograft ACL reconstruction. It has also shown efficacy in decreasing the infection rate in other types of grafts and also in patients with concomitant ligament procedures or open surgeries. However, the lack of high level evidence and the heterogeneity of the different studies makes not feasible to recommend Vancomycin presoaking of the graft universally for every ACL reconstruction patient.

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