Cryopreserved Homografts in Infected Infrainguinal Fields are Associated with Frequent Reinterventions and Poor Amputation Free Survival

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Abstract

Objective:

Single-length saphenous vein continues to be the conduit of choice in infected-field critical limb ischemia (CLI). However, half of these individuals have inadequate vein secondary to previous use or chronic venous disease. We reviewed our outcomes of infected-field infrainguinal bypasses performed with cryopreserved homografts (CH), a widely-accepted alternative to autogenous vein in this setting.

Methods:

This is a retrospective, institutional descriptive analysis of infected-field infrainguinal revascularizations between 2012-2015.

Results:

Twenty-four operations were performed in the same number of patients for limb ischemia with signs of active infection. The mean age of the cohort examined was 62.5 ± 14.4 (standard deviation) years. Mean SVS risk score was 3.9 with a baseline Rutherford's chronic ischemia score of 4.3 at presentation. Emergent procedures constituted 29% of cases and the remainder were urgent. The CH bypass captured was a reoperative procedure in all but one of the patients. Culture positivity was present in 75% of cases with *S. aureus* (29%) the most commonly isolated organism.

30-day mortality and major adverse cardiovascular events were both 4%. Amputation free survival (AFS) was 75% at 30-days. Similarly, 30-day reintervention was 38% with debridement (43%) and bleeding (29%) the most common indications.

Average duration of follow-up was 27.9 ± 20.4 months (range 0.5 – 60.4). Mean length of stay was 14.8 days. Reinfection requiring an additional procedure or antibiotic regimen separate from the index antibiotic course was 13%. Primary patency and AFS at 1-year was 50% and 58%, respectively. Primary patency and AFS at 2-years was 38% and 52%, respectively. Limb salvage at one and 2-years was 70% and 65%. Fifteen (63%) patients required reintervention during the follow-up period with 40% of those subjects undergoing multiple procedures.

Conclusions:

CHs remain a marginal salvage conduit in the setting of infection and no autogenous choices. Therefore, clinicians should individualize usage of this high-cost product in highly selected patients only.

67 **Introduction**

68

69 Autogenous single-length vein continues to remain the gold standard conduit for lower
70 extremity infected-field revascularizations for critical limb ischemia (CLI).[1] However, up to 45% of
71 patients who require bypass do not have adequate continuous vein secondary to chronic venous
72 disease or previous vein harvest.[2,3] Unfortunately, the use of alternative synthetic conduits such as
73 PTFE (polytetrafluroethylene) puts the patient at increased risk for graft infection and limb loss.
74 Therefore, cryopreserved autologous homografts (CHs) have become a popular alternative in the
75 infected surgical field. The purpose of this retrospective analysis was to define outcomes for
76 contemporary use of CHs in infected fields with respect to patency and limb salvage.

Methods

After obtaining Indiana University Institutional Review Board (IRB) approval, a single-center retrospective review was completed of all infected-field CHs implanted for infrainguinal arterial disease from 2012 to 2015. All procedures were performed at one institution by a group of nine academic surgeons. Patients not seen by a vascular surgeon in our system for 12-months were deemed lost to follow-up; for those, contact by phone was attempted.

Demographics captured included age, sex, disease severity, and relevant comorbidities. Presence of infection was defined as observation of cellulitis overlying a bypass graft or perigraft purulence/fluid/air on imaging. Operative characteristics captured included location of proximal/distal anastomosis, muscle flap usage, and intraoperative cultures. Post-operative management strategies queried included use of anticoagulation, antiplatelets, and antibiotics duration.

CHs implanted were kept on-site in a liquid nitrogen dewar. These conduits were prepared per manufacturer's instruction but not routinely seromatched to the host. Based on availability and surgeon preference, the choice of cryopreserved vein or artery was made on a case-by-case basis. CHs were used as the first choice in infected fields during this time over rifampin soaked prosthetic and spliced autogenous vein if continuous vein was not available. All infected fields were copiously irrigated with antibiotic and saline solution. No antibiotic impregnated beads were implanted in our series.

After surgery, all patients maintained IV or PO antibiotic use depending on the clinical severity of infection. In general, it was our practice to extend antibiotics to 4-weeks before a

102 decision on additional duration was made in the outpatient setting. Post-operative imaging,
103 vascular labs, and overall management was left to the discretion of the individual attending
104 surgeon. Most commonly, a post-operative wound check was scheduled two to four weeks after the
105 index procedure. Graft surveillance was scheduled for every three months for the first year
106 followed by every six months thereafter. After the second year of follow-up, patients were
107 extended to annual visits if the bypass remained patent.
108
109 Events captured included one and 2-year primary patency by vascular labs or CTA, one and
110 2-year amputation free survival (AFS), reinterventions, reinfection, anastomotic bleeding,
111 mortality, and major adverse cardiovascular events (MACE). AFS was defined as freedom from all-
112 cause mortality or above-ankle amputation. Reinfection was defined as any decline in clinical
113 status secondary to a new or persistent infection resulting in escalation of antibiotics, drainage, or
114 reoperation to revise the index bypass graft.

Results

From 2012 to 2015, 24 infrainguinal CH (33% vein) bypasses were performed secondary to an infected conduit (n=23) or native artery (n=1). The mean age of our population was 62.5 ± 14.4 years (**Table 1**). The most common comorbidities included previous bypass (96%), HTN (92%), active smoking (58%), HLD (54%), CAD (42%), and DM (25%).

Indications

Twelve percent of the patients were referred acutely after initial evaluation by an outside vascular surgeon for definitive management. Mean Rutherford's chronic limb ischemia score and mean SVS risk score were 4.3 and 3.9, respectively.[4,5] Emergent procedures (performed within 6 hours of admission) constituted 29% of cases and the remainder were urgent (within 24 hours). All patients demonstrated signs of local infection on physical exam or imaging; however, only 8% were septic at the time of presentation. All but one of the procedures were performed as a repeat bypass. This exception was a male with a primary infection of the superficial femoral artery secondary to chronic IV drug use and accidental arterial injection.

Intra-operative

Most of the infections were located in the groin (66.7%). All proximal sites of anastomosis were distal to the external iliac artery. Distal targets were divided into tibioperoneal (17%), below-knee (4%), and above-knee (79%) categories. Three patients received an extranatomic bypass consisting of two obturator bypasses and a femoral to femoral bypass via a retrorectus tunnel. Upon exploration, 33% of the patients had a pseudoaneurysm at the presumed site of infection

(**Table 2**). The majority (92%) of the infected conduits were unincorporated into the soft tissue. Frank purulence was noted in 46% of limbs. Complete graft explantation was completed in 61%, and the remainder received a partial explant at the location of active infection. Rotational muscle flaps were utilized in 46% of cases. Seventy-five percent of cultures returned an identifiable organism (**Table 3**). The most common isolated organisms were *S. aureus* (29%), *P. aeruginosa* (24%), and coagulase negative Staphylococcus (24%). Eighteen percent of positive cultures further demonstrated extended spectrum antibiotic resistance.

Post-operative and 30-day Outcomes

After the index operation, 38% of patients received therapeutic anticoagulation while 88% received antiplatelet therapy (**Table 4**). All subjects received either IV (92%) or PO antibiotics in the peri-operative period. The average duration of antibiotic coverage after surgery was 4.6 weeks. 30-day AFS was 75% with a mortality rate of 4%. The lone death occurred in an individual presenting with peri-graft fluid and sepsis. Antibiotic sensitive S. aureus was isolated from cultures, but the patient continued to decline clinically resulting in multi-system organ failure and eventual withdrawal of care by the family. One patient experienced stroke/MI, suffering from an NSTEMI several days post-operatively. Three (13%) patients experienced anastomotic bleeding with two requiring takebacks for exploration. Reintervention at 30-days was 38% (n=7) most commonly for further debridement (4/7) or bleeding (2/7). Average length of stay was 14.8 days.

Overall Outcomes

Mean follow-up for our population was 27.9 ± 20.4 months (**Table 5**). Primary patency in our population at one and 2-years was 50% and 38%. AFS at one and 2-years was 58% (6

amputations, 5 deaths) and 50% (7 amputations, 7 deaths). Limb salvage at one and 2-years was 70% and 65%, respectively. Reintervention rate during follow-up was 63% with 40% of these patients requiring repeat bypass. The most common cause of reintervention was for stenosis or occlusion; one third of reinterventions were for debridement or drainage. There were no additional episodes of anastomotic bleeding during long-term follow-up compared to the three observed within 30-days. Thirteen percent of patients had reinfection of the implanted CH. Seven patients (29%) required major amputation (3 BKA, 4 AKA) during follow-up. More than half, 54% of all treated patients died during the follow-up period (**Figure 1**). Of these 11 deaths, 4 were from unknown causes outside of our hospital system. The remainder of deaths occurred secondary to lung cancer (n=1), hepatic failure (1), pulmonary embolism (1), renal failure (2), and sepsis (2).

175 **Discussion**

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177 The optimal management strategy for an infected lower extremity bypass graft or artery
178 would be complete excision and in-line reconstruction with continuous autogenous vein.
179 Unfortunately, availability of suitable vein having adequate caliber and length is lacking in many
180 vascular patients with a previous history of bypass.[6] In our cause, this was 96% of the population
181 studied. As such, we routinely employ the use of CHs if the operation involves a potentially infected
182 field. However, we do not routinely implant CHs for sterile-field bypasses given their dismal
183 patency and limb salvage rates.[7-10]

184

185 CHs are harvested from multi-organ donors and preserved in dimethyl sulfoxide (DMSO)
186 before being frozen in liquid nitrogen (-196°C) for storage.[11] Additionally, each CH vendor employs
187 a unique preservation process to decrease antigenicity. The complex harvest and preservation
188 process does incur a significant financial burden to the patient when this conduit is selected for
189 bypass.[12] When needed, grafts are thawed to room temperature and individually modified by the
190 surgeon. After pressurization, the endothelial layer is slowly effaced and the tunica media
191 infiltrated by leukocytes resulting in chronic fibrosis.[13] This smoldering inflammatory response
192 likely has a large role in late graft failure characterized by intense fibroplasia.[14]

193

194 CHs seem to be more resistant to infection than prosthetic materials through an unclear
195 mechanism. This effect has been postulated to be related to the presence of the conduit
196 extracellular matrix allowing for the increased transfer of leukocytes and antibiotics into the
197 perigraft space.[15] Alternatively, it may be related to vendor-unique methods of tissue processing
198 including the storage of grafts in the presence of antibiotics.[16]

199

We report one and 2-year patencies of 50% and 38% corresponding to limb salvage rates of 70% and 65%. AFS during the same time periods were 58% and 52%. Seven patients required amputation of the ischemic limb during the follow-up phase; however, amputation risk was frontloaded as all but one of the subjects lost their limb within 21 days of the index operation. This data clearly suggests a danger period for limb loss in the perioperative phase of infected-field repeat bypasses.

Surprisingly, robust contemporary series describing CH conduits in infected fields have been few and small.[10,17] Brown *et al*. reviewed their experience with CHs in infected fields which included peripheral, but also, carotid and visceral non-aortic reconstructions. Their published experience described 39 total cases with a mean follow-up of 18 months. Mortality at 30-days was 2.6%. Interestingly, graft reinfection did not occur in their population in contrast to our observed rate of 13%. Unfortunately, their 1-year patency was not published.[7] The largest series of cryopreserved vein bypasses was reported in 2003 of 240 consecutive cases in both clean and infected fields. The majority (89%) were performed for rest pain or tissue loss. The percentage of infected limbs were not published. The authors did note an overall 30% 1-year primary patency and 80% limb salvage for all comers.[8]

We found a high reintervention rate of 63% in our study. Twenty-eight additional reinterventions following the index procedure were documented in our 24 patients. The most common indication was for stenosis, occlusion, or necrotizing soft tissue requiring a combination of angioplasty, thrombectomy, redo bypass, and debridement. It seems apparent that the index bypass for this indication cannot be considered the final and definitive operation. Therefore, before selecting the patient for limb salvage or primary amputation, it is imperative to disclose the risk of prolonged hospitalization and additional interventions. Based on our experience, we have adopted

the use of cryopreserved homografts in infected fields with concurrent placement of a muscle flap when possible for the sole purpose of limb salvage. After clearance of the infection, consideration should be made into reoperation with an alternative conduit to improve long-term outcomes.

Unfortunately, the retrospective nature of this study makes it impossible to be sure all adverse events were tracked and captured. As many patients were referred to us from outside vascular surgeons and hospital systems – their follow-up often occurred external to our records. Regardless, the limited adverse events abstracted in this study illustrates well the poor prognosis of this population. Another potential confounder present is inherent to a group practice, where multiple vascular surgeons perform operations per their expertise, often on the same patient. Thus, standard protocol and procedure were lacking.

236 **Conclusion**

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238 CHs are an accepted alternative to continuous autogenous vein for redo bypasses in the
239 setting of an infected field. However, the surgeon should be aware of the increased incidence of
240 amputation, death, and reintervention prior to offering CH limb salvage for this difficult population.

241 **Disclosures**

242

243 The authors have no conflicts of interest to disclose.

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Legends

Table 1: Comorbidities

Table 2: Operative characteristics

Table 3: Culture results

Table 4: Peri-operative management and results

Table 5: Extended outcomes

Figure 1: Kaplan-Meier analysis for AFS over time for patients receiving cryopreserved homografts in an infected surgical field. The inputs displayed are all-cause mortality and major (above-ankle) amputation.

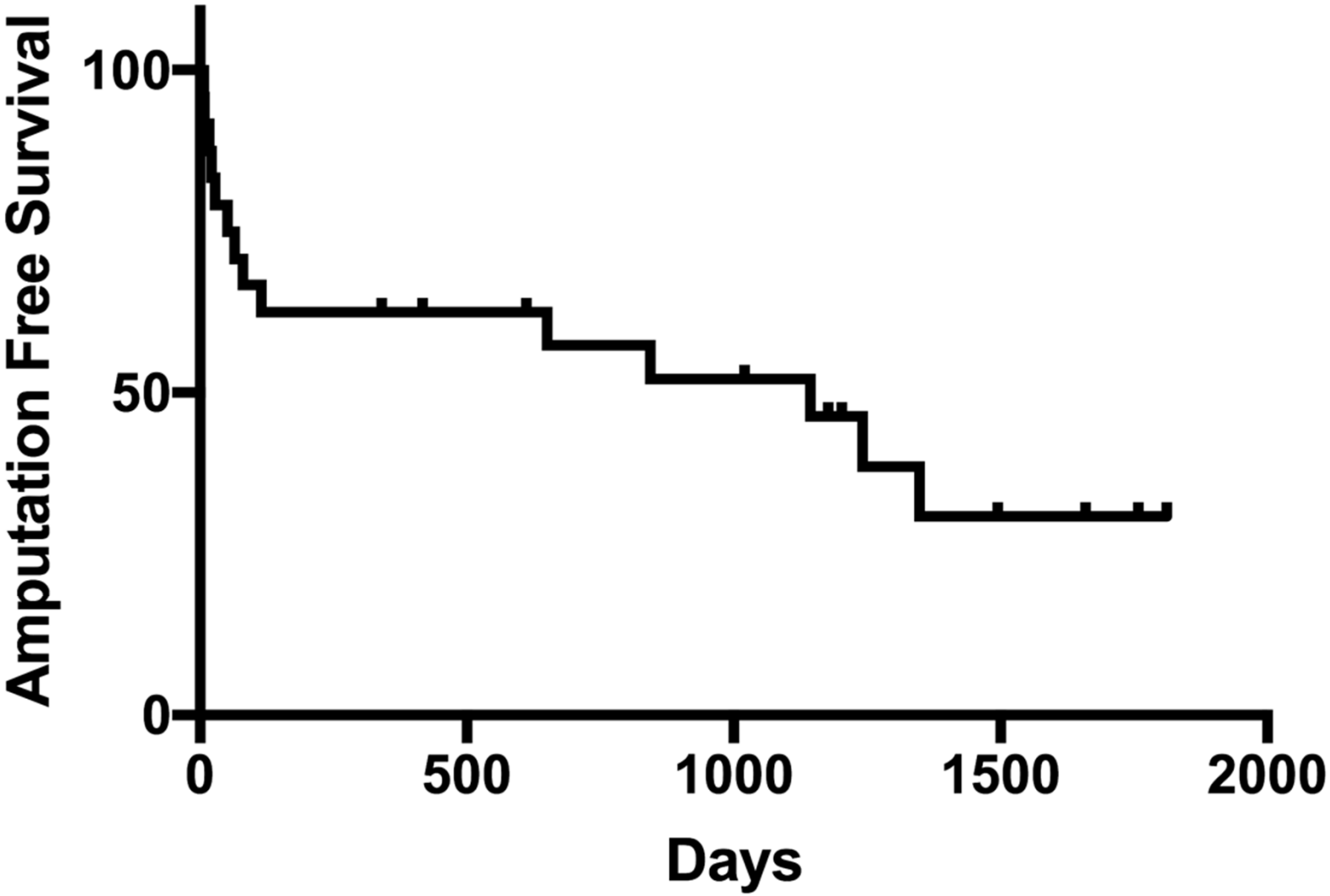
Comorbidity	Incidence
HTN	92%
Active Smoker	58%
HLD	54%
CAD	42%
Obesity	33%
DM	25%
CRI (Cr > 1.5)	21%
CVD	17%
Arrhythmia	17%
HD	13%
COPD	8%
Rutherford's Ischemia Score	4.3 ± 0.6
SVS Risk Score	3.9 ± 2.1

Operative Characteristics	Incidence
Emergent	29%
Septic	8%
Loss of Incorporation	92%
PSA	33%
Purulence	46%
Wound Culture Positive	75%
Muscle Flap	46%

Patient #	Graft Material	Culture Results	ESBL/MRSA
1	Synthetic	S. aureus, S. marascens	No
2	Synthetic	Coagulase^{-} Staph	No
3	Synthetic	Coagulase^{-} Staph, P. aeruginosa, Citrobacter	No
4	Synthetic	P. aeruginosa	No
5	Synthetic	S. aureus	Yes
6	Synthetic	Klebsiella	No
7	Vein	P. aeruginosa	Yes
8	Synthetic	S. aureus, Enterococcus	No
9	Synthetic	Coagulase^{-} Staphylococcus	No
10	Synthetic	S. aureus	No
11	Synthetic	Corynebacterium	No
12	Native Artery	P. aeruginosa	No
13	Synthetic	Corynebacterium	No
14	Synthetic	S. aureus	Yes
15	Synthetic	Coagulase^{-} Staphylococcus	No
16	Synthetic	Enterococcus	No
17	Synthetic	Corynebacterium	No

Post-Operative Regimen	Incidence
Antiplatelets	88%
Anticoagulation	38%
Antibiotics	100%
Antibiotic Duration	4.6 ± 2.2 Weeks
30-day Outcomes	**Incidence**
MACE	4%
Major Amputation	21%
Mortality	4%
AFS	75%
Bleeding	13%
Reintervention	38%

Long-Term Outcomes	Incidence
Follow-up	27.9 ± 20.4 Months
LOS	14.8 ± 16.3 Days
Primary Patency	17.4 ± 18.2 Months
1-yr Primary Patency	50%
1-yr AFS	54%
2-yr Primary Patency	38%
2-yr AFS	52%
Reintervention Rate	63%
Reinfection	13%
Bleeding	13%
Major Amputation	29%
Death	54%


Amputation Free Survival
100
50
0
0
500
1000
1500
2000
Days