

38

Abstract

39

Objectives:

41 The accepted treatment for acute limb ischemia (ALI) is immediate systemic anticoagulation and
42 timely reperfusion to restore blood flow. In this study, we describe the retrospective assessment of
43 pretransfer management decisions by referring hospitals to an academic tertiary care facility and its
44 impact on perioperative adverse events.

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Methods:

47 A retrospective analysis of ALI patients transferred to us via our Level I Vascular Emergency
48 program from 2010 to 2013 was performed. Patient demographics, comorbidities, Rutherford ischemia
49 classification, time to anticoagulation, and time to reperfusion were tabulated and analyzed for correlation
50 to incidence of major adverse limb events (MALE), mortality, and bypass patency in the perioperative
51 period (30-day postoperative). All time intervals were calculated from the onset of symptoms and
52 categorized into three subcohorts (<6 hrs, 6-48 hrs, and >48 hrs).

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Results:

55 Eighty-seven patients with an average age of 64.0 (\pm 16.2) years presented to outlying hospitals
56 and was transferred to us with lower extremity ALI. The mean delay from symptom onset to initial
57 referring physician evaluation was 18.3 hrs. At that time of evaluation, 53.8% had Rutherford class IIA
58 ischemia and 36.3% had class IIB ischemia. Seventy-six (87.4%) patients were started on heparin
59 previous to transfer. However, only 44 (57.9%) patients reached therapeutic levels as measured by
60 activated partial thromboplastin time (aPTT) prior to definitive revascularization. A delay of
61 anticoagulation initiation >48 hrs from symptom onset was associated with increased 30-day
62 reintervention rates compared with the <6 hrs group (66.7% vs. 23.5%; $p<0.05$). However, time to
63 reperfusion had no statistically significant impact on MALE, 30-day mortality, or 30-day interventional

64 patency in our small cohorts. Additionally, patients with a previous revascularization had a higher 30-day
65 reintervention rate (46.5%; $p<0.05$).

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67 **Conclusions:**

68 The practice of timely therapeutic anticoagulation of patients referred for ALI from community
69 facilities occurs less frequently than expected and is associated with an increased perioperative
70 reintervention rate.

71 **Background**

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73 Paramount to the treatment of ALI is prompt diagnosis, anticoagulation, and timely
74 revascularization to minimize the risk of limb loss.¹ Unfortunately, delays in diagnosis and treatment
75 continue to be a significant challenge, especially in those who are initially evaluated at a community
76 hospital without dedicated vascular specialists.² Our Level I Vascular Emergency program was initiated
77 in 2009 as part of an effort to improve vascular outcomes in the State of Indiana. Transferring facilities
78 state the diagnosis, hospital location, and urgency of pathology. All patients stable enough for transfer
79 are accepted, and transportation is accomplished by ground or air at the discretion of the accepting
80 physician and weather conditions.

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82 Although revascularization strategies and outcomes are well studied, there is a relative dearth of
83 knowledge regarding the effect of preintervention anticoagulation with timely triage and their effects on
84 limb salvage and mortality.³ Therefore, the purpose of this study was to review our three-year
85 experience, immediately after initiation of the Level I program, with the pretransfer care of ALI patients
86 at our tertiary referral center and the outcomes associated with deviations from defined ideal
87 management.

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Methods

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90 After approval from the Indiana University Institutional Review Board (IRB), we performed a
91 retrospective analysis of a prospectively maintained database of all patients diagnosed with ALI
92 transferred to our facility via our Level I program from Jan 2010 to August 2013. For purposes of this
93 study, ALI was defined as a cold, painful, ischemic limb presenting within a week of symptom onset.^{4,5}

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95 Patient demographics, comorbidities, Rutherford ischemia severity, time to heparinization, time
96 to revascularization, and postoperative outcomes were abstracted via review of medical records. Times to
97 emergency room (ER) presentation, heparin initiation, and revascularization were all recorded from the
98 time of symptom onset and arbitrarily categorized into three subgroups (<6 hrs, 6-48 hrs, and >48 hrs).
99 Our 30-day outcomes of interest were major amputation (above ankle), interventional patency, need for
100 vascular reinterventions, and mortality. Categorical variables were compared with Fisher's exact tests
101 while continuous variables (\pm standard deviation) were compared with Student's T-tests at an α of 0.05.

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Results

Comorbidities

In the three years queried, 103 patients with limb ischemia were transferred to us as a Level I Vascular Emergency; patients presenting with upper limb ischemia were excluded leaving 87 remaining cases. Demographics and comorbidities of the study population are detailed in **Table 1**. The average age of our population was 64.5 (\pm 16.2) years with a slight predisposition towards the male gender (57.5%). The most common comorbidity in this population was CAD (70.7%). Atrial fibrillation, a frequent source of thromboembolism to the extremities, was present in 20.1% of subjects. Additionally, 39.0% of the patients had a previous history of ipsilateral vascular bypass and 40.2% were actively smoking at the time of ALI onset.

Preinterventional Management

The mean duration of time from symptom onset to initial outside hospital (OSH) evaluation was 18.3 hrs (range = 1-118 hrs, median = 6 hrs). At the time of evaluation by the first physician, 53.8% had Rutherford class IIA ischemia and 36.3% had class IIB ischemia. The average delay from initial OSH evaluation to evaluation by a tertiary care hospital physician was 3.0 hrs (median = 2.0 hrs). After arrival to our facility from a mean transfer distance of 48.0 miles (range 1-183 = miles, median = 47 miles), mean delay until definitive blood flow restoration was 9.5 hrs (median = 5.0 hrs).

Among the 76 (87.4%) patients who received systemic heparin previous to transfer, only 44 (57.9%) reached a documented therapeutic aPTT before their operation (**Table 2**). Of the remaining anticoagulated patients, 13 maintained nontherapeutic aPTTs while 19 patients did not have an aPTT measured before revascularization. Of those without a documented aPTT, 89.5% presented emergently

128 for IIB ischemia and had intraoperative activated clotting times (ACT) on record. Of note, only 10
129 (11.5%) patients received heparin and were documented therapeutic by aPTT in less than 6 hrs from
130 symptom onset. Eleven (12.6%) patients were not anticoagulated at all after presentation to the
131 transferring facility. The reasons for not starting anticoagulation were unclear in all cases; however, two
132 patients clearly did not have a salvageable limb. There were no differences between patients with IIA and
133 IIB ischemia in terms of delays to heparin initiation ($p=0.25$) or revascularization ($p=0.47$).

134

135 ***Intervention***

136 Arterial flow was restored in only three (3.4%) patients via a completely percutaneous approach.
137 All three patients were in IIA ischemia at presentation and consisted of one with an acutely thrombosed
138 PTFE graft who was thrombolysed and two occlusions of the iliac and superficial femoral arteries treated
139 by angioplasty and stenting. The remaining revascularizations utilized a primarily open technique. Of
140 these patients, 50 (59.5%) required primary thromboembolectomy while 28 (33.3%) patients required a *de*
141 *novo* lower extremity vascular bypass. Only 12.6% of the total study population was revascularized
142 within 6 hrs of symptom onset. However, in the IIB ischemia subcohort, 36.3% was revascularized
143 within 6 hrs of symptom onset.

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145 ***30-day Major Adverse Events***

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147 ***Major Amputations:***

148 The 30-day major amputation rate for all transferred ALI patients was 13.1% (**Table 3**). Time to
149 anticoagulation did not affect amputation risk. We did not observe a difference between Rutherford IIA
150 and IIB patients ($p=0.43$); however, both groups experienced a lower amputation rate compared to those
151 presenting with class III ischemia ($p<0.01$). A history of an ipsilateral revascularization did not influence
152 amputation risk ($p=0.49$). Delays to therapeutic aPTT and revascularization did not influence
153 perioperative major amputation rates in our population.

154

155 *Reinterventions:*

156 The overall 30-day vascular reintervention rate was 36.8%. We observed a difference in
157 reintervention based on time to systemic heparinization with the >48 hrs cohort experiencing a 66.7%
158 event rate compared to a 23.5% in patients heparinized in <6 hrs ($p<0.05$). Patients who had a previous
159 ipsilateral revascularization were at a higher risk of reintervention (46.7% vs 36.8%, $p<0.05$). No
160 difference was observed between class IIA and IIB ischemia patients. Those who delayed ER
161 presentation (>48 hrs) also were at greater risk for perioperative reintervention ($p<0.05$). Delays until
162 therapeutic aPTT and revascularization did not influence perioperative vascular reintervention risk.

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164 *Patency:*

165 The overall 30-day interventional patency rate was 72.2%. There was no difference based on
166 delay to heparinization; although, a nonsignificant inferior patency rate was noted in the >48 hrs cohort
167 compared to the minimal delay cohort (60% vs 76.5%, $p=0.42$). Additionally, we observed no difference
168 between class IIA and IIB patients. There was also no difference based on delay to ER presentation or
169 presence of previous ipsilateral bypass. Delays until therapeutic aPTT and revascularization did not
170 influence perioperative patency.

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172 *Mortality:*

173 The overall 30-day mortality was 7.9%. The most common cause of death was septic shock
174 ($n=3$) followed by myocardial infarction ($n=1$), multiorgan systems failure ($n=1$), and acute mesenteric
175 ischemia ($n=1$). While there was no statistical difference in mortality by time to anticoagulation, a trend
176 was observed. All patients who were heparinized without delay survived, compared to a 10.0% mortality
177 ($p=0.28$) in the 6-48 hrs group and 13.3% ($p=0.20$) in the >48 hrs group. The degree of Rutherford
178 ischemia did not seem to affect perioperative mortality in our population. Similarly, delays until
179 therapeutic aPTT and revascularization did not influence perioperative mortality.

180

Discussion

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182 In ALI, a sudden cessation of arterial blood flow directly blocks nerve, soft tissue, and
183 musculoskeletal access to resources vital to cell survival.⁶ In this setting, a patient has approximately six
184 hours for restoration of blood carrying oxygen and nutrients before irreversible functional damage
185 occurs.⁷ However, the duration until irreversible damage is dependent on tissue conditioning and degree
186 of collateralization from preexisting baseline vascular disease.⁸ Therefore, clinical scoring systems are
187 utilized to predict disease severity to guide treatment individualization.⁹ Of particular importance is the
188 Rutherford ALI categorization system, an easy to use clinical tool which classifies ischemia severity and
189 guides urgency to revascularization.⁵

190

191 The latest ALI consensus practice guideline was developed in conjunction with the Society of
192 Vascular Surgery, American Heart Association, Intersociety Consensus for the Management of Peripheral
193 Arterial Disease, and representative bodies of cardiology, radiology, and vascular medicine. In these
194 guidelines, only four level I recommendations pertain to the preoperative care of the ALI patient
195 **(Figure)**.¹⁰ At the time of presentation to any facility, patients suspected of ALI should be evaluated by
196 an experienced clinician comfortable with the assessment of limb viability and can implement immediate
197 medical therapy. At that time, a comprehensive history should be taken to determine the cause of
198 thrombosis or embolization. Additionally, the initial evaluation should focus on the rapid assessment of
199 1) limb viability and 2) potential for salvage. It is key to note that this assessment does not require
200 imaging, especially if it may delay appropriate triage. After diagnosis, prompt systemic anticoagulation
201 should be initiated unless a hard contraindication is present.¹¹

202

203 The use of any antiplatelet and/or anticoagulant must be communicated clearly and concisely by
204 the transferring team. Especially important details to include are time of medication initiation and dose.
205 In our review, 13 patients received heparin without documentation of initiation time by the transferring

206 team. Additionally, 11 patients did not receive heparin at the transferring facility at all. While two limbs
207 were clearly nonsalvageable, none of these 11 patients had a clear contraindication on retrospective chart
208 review. While a possible explanation may be an attempt to avoid coagulopathy during surgery by
209 clinicians uncomfortable with preoperative anticoagulation, the short half-life of unfractionated heparin
210 makes cessation of medication administration on the way to the OR an ideal therapeutic plan.¹² We
211 observed a trend of increasing mortality in those who had a delay until systemic heparinization. This
212 effect may prove to be significant with a higher-powered study. Failure to anticoagulate in the ALI
213 population is not an isolated problem for our facility; an European experience reported by Spanos *et al*
214 reported their four-year experience of 112 consecutive ALI patients and found that only 67% of them
215 were anticoagulated at the time of arrival after transfer.¹³ A concerted effort should be made to
216 emphasize the importance of prompt anticoagulation to our transferring colleagues.

217
218 The superior outcomes observed in ALI patients who received timely anticoagulation occurred
219 regardless of their aPTT status in our study, thus underscoring the importance of anticoagulation and less
220 so the emphasis on clotting times in limb salvage. We did not observe a significant difference in
221 outcomes with regards to perioperative mortality, patency, and major amputation in those who had a >48
222 hr delay to heparinization. However, this was almost certainly due to lack of power as clinical experience
223 would dictate a morbid clinical course in these patients. Unless contraindicated, the best anticoagulant in
224 the acute setting is IV unfractionated heparin.¹⁴ The dosing of which is discussed in detail elsewhere.¹⁵
225 Despite limitations, aPTT remains the most convenient and frequently used method for monitoring *in vivo*
226 heparin response. It should be measured minutes after initial medication bolus to confirm therapeutic
227 effect and continuously monitored to gauge needed changes to the continuous rate.¹⁶

228
229 A problem we encountered in our cohort was a significant delay in presentation to the initial
230 hospital of more than 18 hours from symptom onset. The worst offenders were those with baseline
231 disease and therefore assumed acute limb pain was a day-to-day variant of symptoms and not a sudden

232 progression of disease. This incorrect assumption often made a difference between the salvage of a
233 functional limb or not. Therefore, the burden is on us, as vascular surgeons, to educate our patients on
234 signs of ischemic progression from chronic disease to ALI in the office setting before it occurs.

235
236 Seven patients (8%) were transferred without documentation of a lower extremity pulse exam in
237 the history and physical of the initial evaluating physician. Not only is this a clinical concern, but it may
238 have serious medicolegal ramifications. A detailed lower extremity vascular exam is standard of care for
239 any patient with limb pain, sensory loss, or motor dysfunction.¹⁷ Although the pulse exam may be
240 subjective, the following classification is recommended at minimum: a) normal, b) weakly palpable, c)
241 doppler signal present, and d) no signal.¹⁸ The status of the dorsalis pedis and posterior tibial arteries on
242 both sides need to be documented in the medical record.

243
244 As is the case for any retrospective review, this study has some inherent limitations.¹⁹ However,
245 a recurring deficit which developed during data collection was the incomplete documentation from the
246 transferring facilities on time of symptom onset, degree of ischemia, and time and effect of
247 anticoagulation despite receiving all available medical records. Consequently, the patient pool for
248 statistical analysis was reduced affecting the power to detect outcome differences. Although we did
249 receive direct transfers from community vascular surgeons, most of the patients arrived from ERs staffed
250 by emergency, family, and internal medicine specialists often uncomfortable with ALI management. As
251 such, it is of utmost importance that the accepting physician clearly state to the transferring physician the
252 treatment plan before, during, and after the transfer process.

253

Conclusion

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255 ALI is a challenging pathology for the vascular surgeon. In many regions, referral of those
256 diagnosed at community hospitals to tertiary centers have become the established system. In this study,
257 we report inferior perioperative outcomes associated with patients who did not receive treatment per ALI
258 practice guidelines. Therefore, improved system-wide protocols in the diagnosis, care, and transfer of
259 these patients are needed to provide safe, timely care.

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Legends**Table 1**

Demographics and comorbidities

Table 2

Delays in treatment

Table 3

Perioperative outcomes by delay until heparinization from symptom onset. Fisher's exact testing was performed comparing the minimally delayed cohort (<6 hrs) to the remaining groups.

Figure

Summary of the latest AHA/ACC consensus practice guidelines

Condition	Incidence
Age	64.5 ± 16.2
Male	57.5%
CAD	70.7%
HTN	67.9%
Active Smoker	40.2%
HLD	37.8%
DM	32.1%
AF	20.1%
COPD	18.3%
Previous Ipsilateral Revascularization	39.0%
Rutherford Classification at Presentation	Incidence
I	7.5%
IIA	53.8%
IIB	36.3%
III	2.5%

Delay to ER Presentation (n=87)	Incidence
<6 hrs	37.9%
6-48 hrs	25.3%
>48 hrs	16.1%
Unknown	20.7%
Delay to Heparin (n=76)	Incidence
<6 hrs	23.7%
6-48 hrs	39.5%
>48 hrs	19.7%
Unknown	17.1%
Delay to Revascularization (n=71)	Incidence
<6 hrs	12.7%
6-48 hrs	69.0%
>48 hrs	18.3%

Delay Until Systemic Heparinization

	<6hr	6-48hr	>48hr
30-day Amputation	16.7%	6.9%	21.4%
		<i>p</i> =0.36	<i>p</i> =1.0
30-day Reintervention	23.5%	32.2%	66.7%
		<i>p</i> =0.74	<i>p</i>=0.03
30-day Mortality	0%	10.0%	13.3%
		<i>p</i> =0.28	<i>p</i> =0.20
30-day Patency	76.5%	74.1%	60%
		<i>p</i> =1.0	<i>p</i> =0.42

Patient Suspected of ALI

Tenet 1

Patients suspected of ALI should be emergently evaluated by a clinician with sufficient experience to determine limb viability and implement appropriate therapy

Tenet 2

A comprehensive history should be obtained to determine the cause of thrombosis and/or embolization

Tenet 3

The initial evaluation should determine 1) limb viability and 2) potential for salvage – it does not require imaging

Tenet 4

Systemic anticoagulation should be initiated immediately, unless a hard contraindication is present