Quality Improvement Guidelines for Percutaneous Management of Acute Lower-extremity Ischemia

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ABBREVIATIONS

ALI = acute limb ischemia, APSAC = antistreplase, MTD = mechanical thromboembolectomy device, PAT = percutaneous aspiration thromboembolectomy, pro-UK = prourokinase, RPA = reteplase, r-UK = recombinant urokinase, SK = streptokinase, STILE = Surgery versus Thrombolysis for Ischemia of the Lower Extremity [study], tPA = tissue plasminogen activator, TOPAS = Thrombolysis or Peripheral Arterial Surgery [study], TNK = tenecteplase, TPA = alteplase, UK = urokinase

PREAMBLE

The membership of the Society of Interventional Radiology (SIR) Standards of Practice Committee represents experts in a broad spectrum of interventional procedures from both the private and academic sectors of medicine. Generally, Standards of Practice Committee members dedicate the vast majority of their professional time to performing interventional procedures; as such, they represent a valid broad expert constituency of the subject matter under consideration for standards production.

Technical documents specifying the exact consensus and literature review methodologies as well as the institutional affiliations and professional credentials of the authors of this document are available upon request from SIR, 3975 Fair Ridge Dr., Suite 400 N., Fairfax, VA 22033.

This standards document is a revision of the original one that first appeared in the *Journal of Vascular and Interventional Radiology* in 2005 (J Vasc Interv Radiol 2005; 16:585–595). This version contains new information, including modified definitions to best reflect the current state of the art.

METHODOLOGY

SIR produces its Standards of Practice documents using the following process. Standards documents of relevance and timeliness are conceptualized by the Standards of Practice Committee members. A recognized expert is identified to serve as the principal author for the standard. Additional authors may be assigned depending on the magnitude of the project.

An in-depth literature search is performed by using electronic medical literature databases. Then, a critical review of peer-reviewed articles is performed with regard to the study methodology, results, and conclusions. The qualitative weight of these articles is assembled into an evidence table (1–40), which is used to write the document such that it contains evidence-based data with respect to content, rates, and thresholds.

When the evidence of literature is weak, conflicting, or contradictory, consensus for the parameter is reached by a minimum of 12 Standards of Practice Committee members by using a Modified Delphi Consensus Method (**Appendix A**) (41). For purposes of these documents, consensus is defined as 80% Delphi participant agreement on a value or parameter. In addition, for the specific purpose of this document, studies with fewer than 50 patients were not included for the purpose of defining the parameters established here later. Generic terms for United States Food and Drug Administration–approved thrombolytic agents accepted by the the United States Adopted Names Council, a consortium sponsored by the United States Pharmacopeial Council, are listed in **Tables 1 and 2** (42).

The draft document is critically reviewed by the Standards of Practice Committee members by telephone conference calling or face-to-face meeting. The finalized draft from the Committee is sent to the SIR membership for further input/criticism during a 30-day comment period. These comments are discussed by the Standards of Practice Committee, and appropriate revisions are made to create the finished standards document. Before its publication, the document is endorsed by the SIR Executive Council.

ACUTE LIMB ISCHEMIA

Acute limb ischemia (ALI), defined as any sudden decrease in, or worsening of, limb perfusion causing a threat to extremity mobility and viability that has been present for less than 14 days, is one sequela of peripheral arterial disease (PAD). It is one of the most common vascular emergencies interventional radiologists and vascular surgeons are asked to evaluate and treat. The treatment options for ALI fall into three broad categories: (i) medical management, (ii) surgical management, and (iii) image-guided minimally invasive therapies. Medical management entails systemic anticoagulation with continued observation, surgical management entails thrombectomy, and image-guided minimally invasive therapies entail percutaneous endovascular removal of the clot. Often, more than one is needed to achieve optimum results. Their relative merit depends on the clinical history and physical findings. Nonetheless, if removal of the clot by any method is chosen, the underlying causative abnormality must be addressed.

There are diverse etiologies for ALI, with the two most common etiologies being embolus and thrombosis in situ secondary to underlying disease such as atherosclerosis (43). Differentiation between the two can

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Table 1. Thrombolytic Agents: Background Information

Generic Name	Brand Name(s)	Manufacturer	Abbreviation
Streptokinase	Streptase; Kabikinase	Dexa Medica/CSL Behring, Marburg, Germany	SK
Anistreplase	Eminase	GlaxoSmithKline, London, UK	APSAC
Human-derived urokinase	Kinlytic; Abbokinase	Microbix Biosystems, Mississauga, ON, Canada	UK
Recombinant urokinase	Urokinase Alfa	Abbott Laboratories, Abbott Park, IL	r-UK
Recombinant prourokinase	Prolyse	Abbott Laboratories, Abbott Park, IL	pro-UK
Alteplase	Activase	Genentech, San Francisco, CA	TPA
Reteplase	Retavase	Centocor, Malvern, PA	RPA
Tenecteplase	TNKase	Genentech, San Francisco, CA	TNK

Table 2. Thrombolytic Agents: Pharmacologic Information

Agent	Abbreviation	Molecular Weight (Da)	Plasma Half-life (min)	Fibrin Specificity	Fibrin Affinity
Streptokinase	SK	48,000	16/90	Low	Low
Anistreplase	APSAC	131,000	70–120 (mean, 90)	Low	Intermediate
Urokinase	UK	32,000-54,000	14	Low	Low
Recombinant urokinase	r-UK	54,000	7	Low	Low
Recombinant prourokinase	pro-UK	49,000	7	High	Low
Alteplase	TPA	68,000	3.5	High	High
Reteplase	RPA	39,000	14	Moderate	Low
Tenecteplase	TNK	65,000	15	Very high	High

sometimes be difficult; the latter is far more common in occluded bypass grafts. ALI is usually caused by atherosclerotic disease but can also arise from other etiologies (eg, dissection, intimal hyperplasia, in situ thrombosis secondary to a hypercoagulable state, trauma, vasculitis, aneurysm thrombosis). Outcomes and prognosis of ALI largely depend on the rapid diagnosis and initiation of appropriate and effective therapy. The 30-day mortality rate is approximately 15%, and there are variable reported amputation rates of 10%–30% (44). For many years, primary surgical intervention was performed, but entailed significant morbidity and mortality (45–47).

Systemic administration of a thrombolytic agent to treat ALI carries a high morbidity and mortality risk with poor clinical outcomes, and is not recommended (48–50). In 1974, Dotter et al (51) reported the feasibility of use of transcatheter streptokinase (SK) infusions for the treatment of arterial and graft occlusions. Since that time, there have been a number of advances in endovascular thrombolytic therapy. Current methods include catheter-directed methods for local delivery of thrombolytic agent, aspiration thrombectomy, mechanical thromboembolectomy, and pharmacomechanical thrombolysis. Successful management of ALI requires optimal patient selection with astute and timely clinical assessment.

Randomized prospective trials have shown that patients with acute leg ischemia (ie, < 14 d) have improved survival and long-term benefit compared with surgery when thrombolysis is used alone or to reduce the magnitude of surgery (8,17,52). Intraarterial catheter-directed administration of thrombolytic agents can achieve thrombolysis of the thrombosed segments and unmask a causative lesion in most cases. This lesion can then often be treated with endovascular techniques. In many patients, thrombolysis with adjunctive procedures can reduce the scope of or even eliminate the need for surgical intervention. Surgical reperfusion therapy is a very high-risk procedure in elderly patients, with surgical mortality rates as high as 29% in high-risk populations (53).

Recommending a single uniform treatment protocol from the numerous clinical studies is not possible because of the wide variability in reporting. Several independent variables have been identified, including (i) acute versus chronic limb ischemia; (ii) target site treated, ie, native vessel or graft; (iii) dosing regimen of the thrombolytic drug and duration of therapy; (iv) method of infusion, ie, continuous infusion versus bolus infusion or other methods; (v) postthrombolytic anticoagulation therapy, eg, heparin or aspirin; and (vi) clinical endpoints, eg, technically successful thrombolysis versus clinically useful thrombolysis versus amputation-free survival. For instance, the Rochester study (7) used "event-free survival," the Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial (8) used "composite clinical outcome," and the Thrombolysis or Peripheral Arterial Surgery (TOPAS) study (17) used "arterial recanalization and extent of lysis."

Although outcome measures in published studies focus on amputation-free survival, for the purposes of quality assurance, a definition of greater clinical relevance was sought. The outcome measures examined in this document are overall clinical success and major complications.

These guidelines were written to be used in quality improvement programs to assess the outcome of percutaneous management of ALI. The most important processes of care are (i) appropriate patient selection, (ii) performance of the procedure, and (iii) monitoring of the patient. Outcome measures are assigned threshold levels.

DEFINITIONS

ALI is defined as any sudden decrease in or worsening of limb perfusion causing a threat to extremity mobility and viability that has been present for less than 14 days (49,54). Thrombolysis is defined for the purposes of this document as the percutaneous treatment of the thrombus with pharmacologic therapy, mechanical therapy, or a combination of the two.

Guide Wire Traversal Test

In the guide wire traversal test, a guide wire is passed through the length of the thrombus before initiation of prolonged infusion. If a wire is passed, thrombolysis for acute (< 7 d) occlusion is thought to be more likely (1,46,55). McNamara and Fisher (1) showed that initial successful thrombolysis was more likely with positive guide wire traversal (100% vs 10%; $P < .01$). This was also observed (89% vs 16%; $P = .003$) by Ouriel et al (45). Failure to pass a guide wire is not an absolute contraindication to thrombolytic therapy, but rather a predictor of poorer outcome.

Regional Intraarterial Infusion

In nonselective regional intraarterial infusion, the catheter through which the thrombolytic agent is delivered is positioned proximal to the occluded

vessel. In selective regional intraarterial infusion, the catheter tip or its infusion segment is embedded in the thrombotic occlusion.

Infusion Methods

Intrathrombus Infusion. In intrathrombus infusion, the thrombolytic agent is delivered by an intraarterial catheter embedded within the thrombus. This position maximizes the concentration of the drug within the thrombus and delivers the drug to the region of thrombus-bound plasminogen. The thrombolytic agent is delivered via a catheter embedded in the clot. The thrombolytic agent exits the catheter via multiple side holes or through the pores of a low-pressure balloon (eg, ClearWay OTW; Atrium Medical, Hudson, New Hampshire).

Intrathrombus "Bolusing" or "Lacing". The term "bolusing" has been used interchangeably with "lacing." These terms refer to the initial intrathrombic delivery of a concentrated thrombolytic agent with a view toward saturating the thrombus with the plasminogen activator before infusion. During this portion of the procedure, a catheter (with an end hole or multiple side holes with or without a tip-occluding wire) is positioned in the most distal part of the thrombus. It is retracted proximally as the thrombolytic agent is delivered along the entire length of the thrombotic occlusion.

Stepwise Infusion. Stepwise infusion entails placement of the tip of the catheter within the proximal thrombus and infusion of a fixed dose of thrombolytic agent over a short period of time. As thrombus dissolves, the catheter is advanced.

Continuous Infusion. Continuous infusion is infusion of thrombolytic agent by using a constant rate (ie, steady flow).

Graded Infusion. Graded infusion entails periodic tapering of the infusion rates, with the highest doses given within the first few hours.

Forced Periodic Infusion. Forced periodic infusion (ie, pulse spray) entails forceful injection of the thrombolytic agent into the thrombus to fragment it and/or create deep crevices/fissures, thereby increasing the surface area available for thrombolytic action.

Pharmacomechanical Thrombolysis. Pharmacomechanical thrombolysis is the combination of mechanical thrombus disruption with concomitant infiltration of a thrombolytic agent with the use of a device (ie, AngioJet; Medrad, Warrendale, Pennsylvania). Isolated thrombolysis is a specific type of pharmacomechanical thrombolysis that entails the use of a device (ie, Trellis, Covidien, Manfield, Massachusetts) with balloons that are inflated—one proximal to the thrombus and the other distal to the thrombus—with infusion and mechanical dispersion of the thrombolytic agent in the isolated arterial segment.

Technical Success. Technical success is defined as restoration of antegrade flow with relief of the acute ischemic symptoms at rest.

Time to Thrombolysis. Time to thrombolysis is measured from onset of thrombolytic infusion to complete recanalization or maximal radiologic thrombolysis (15).

Complete Thrombolysis. Complete thrombolysis entails clearance of an occluded vessel by thrombolytic therapy with complete angiographic clearance of thrombus from an occluded vessel by thrombolytic therapy as determined by follow-up angiography. The underlying lesion may still be present (15).

Thrombolytic Failure. Thrombolysis failure is the absence of clinically useful thrombolysis (15). Clinically useful thrombolysis entails relief of the acute ischemic symptoms or reduction of the level of the subsequent surgical intervention or amputation needed (**Table 3**) (49).

Overall Clinical Success. Overall clinical success entails relief of the acute ischemic symptoms and return of the patient to at least his/her preocclusive clinical baseline level after the removal of thrombus and performance of adjunctive procedures (49).

Major Hemorrhage. Major hemorrhage is a hemorrhage of sufficient magnitude that it leads to (i) extended or unexpected hospitalization, (ii) surgery to arrest the hemorrhage, or (iii) the need for blood transfusion of two or more units. Intracranial hemorrhage of any size and hemorrhages that result in death are major hemorrhages by definition.

Thresholds: Outcome and Major Complications

Although practicing physicians should strive to achieve perfect outcomes (eg, 100% success, 0% complications), in practice, all physicians will fall short of this ideal to a variable extent. Therefore, indicator thresholds may be used to assess the efficacy of ongoing quality improvement programs. For the purposes of these guidelines, a threshold is a specific level of an indicator that should prompt a review. "Procedure thresholds" or "overall thresholds" reference a group of indicators for a procedure, such as major complications. Individual complications may also be associated with complication-specific thresholds. When measures such as indications or success rates fall below a (minimum) threshold, or when complication rates exceed a (maximum) threshold, a review should be performed to determine causes and to implement changes, if necessary. For example, if the incidence of intracranial hemorrhage is one measure of the quality of pharmacologic thrombolysis, values in excess of the defined threshold, in

Table 3. Recommended Scale for Gauging Changes in Clinical Status in ALI after Thrombolysis (49)

Score	Description
−1	Ischemia worse (by ≥ 1 major/minor category from SVS/ISCVS clinical categories of ALI)
0	No change (failure)
+1	Ischemia improved*
	a. Revascularization with thrombolytic methods alone
	I. Amputation necessary but at a lesser level†
	b. Adjunctive surgical revascularization necessary but at a lesser level‡
	I. Amputation necessary but at a lesser level†
	c. Adjunctive endovascular revascularization necessary (eg, angioplasty, stent, atherectomy)
	I. Amputation necessary but at a lesser level†

ALI = acute limb ischemia, SVS/ISCVS = Society for Vascular Surgery/International Society for Cardiovascular Surgery.
* Categories a, b, and c do not imply greater or lesser degrees of success.
† Levels of amputation: 1, above the knee; 2, below the knee; 3, transmetatarsal; and 4, toe.
‡ Levels of surgical revascularization: 1, major (insertion of new bypass graft, replacement of existing bypass graft, or excision or repair of aneurysm); 2, moderate (graft revision, patch angioplasty, endarterectomy, or profundaplasty); 3, minor (thrombectomy/embolectomy or fasciotomy).

this case 2%, should trigger a review of policies and procedures within the department to determine the causes and to implement changes to lower the incidence of the complication. Thresholds may vary from those listed here; for example, patient referral patterns and selection factors may dictate a different threshold value for a particular indicator at a particular institution. Therefore, setting universal thresholds is very difficult, and each practice group is urged to alter the thresholds as needed to higher or lower values to meet its own quality improvement program needs.

Complications can be stratified on the basis of outcome. Major complications result in an unplanned increase in the level of care, prolonged hospitalization, permanent adverse sequelae, or death. Minor complications result in no sequelae or may require nominal therapy (**Appendix B**). The complication rates and thresholds described herein refer to major complications.

INDICATIONS/PATIENT SELECTION

Patient selection is determined by a number of clinical findings of the limb in question (**Tables 4, 5**) (43,49,56,57). Patients can usually relate their deterioration of symptoms to a particular time period. An appropriate history and physical examination and an evaluation of the patient for absolute and relative contraindications to thrombolytic therapy should be performed. The history should focus on when, where, and what events surrounded the ALI symptoms. The patient should be evaluated for pain, sensory deficit, numbness, paresthesia, decreased motor function, pallor, and decreased temperature. Laboratory tests should be obtained to assess for renal function, baseline hematocrit and coagulation profile, and evidence of hyperkalemia and acidosis. An electrocardiogram may be obtained to ascertain if any cardiac arrhythmias are present and to assess for a recent myocardial infarction. Doppler examination of the limb should be obtained when possible.

If possible, it is also important to try to determine the etiology of ALI, whether it is embolic or thrombotic (**Table 6**) (43). This will affect immediate and long-term management. In an embolic event, the heart is the source in 80%–90% of cases (58,59), with a majority of these having underlying myocardial disease. Arrhythmias, such as atrial fibrillation, can have a 3%–6% annual risk of thromboembolic complications if they are not treated with anticoagulation (60). In cases of an embolic event, the symptoms are often of sudden onset and severe, and these patients may be

Table 4. Clinical Manifestation of Acute Arterial Embolism versus Thrombosis (43)

Embolism	Thrombosis
Arrhythmia	No arrhythmia
Sudden onset	Sudden or slower onset
Severe signs and symptoms	Less severe signs and symptoms
No history of claudication or rest pain	History of claudication, rest pain
No risk factors for peripheral arterial disease*	Risk factors for peripheral vascular disease
Normal contralateral pulse exam	Abnormal contralateral pulse exam
No physical findings of chronic limb ischemia	Physical findings of chronic limb ischemia†

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* Factors include, eg, cardiac disease, previous myocardial infarction, hyperlipidemia, stroke, family history, history of smoking, diabetes.

† Absence of extremity pulses, diminished hair growth, thin skin, thick nails, and ulcers.

Table 5. Clinical Categories of Acute Limb Ischemia (56,57)

Category	Description	Prognosis	Findings			Doppler Signal	
			Sensory Loss	Motor Deficit	Arterial	Venous
I	Viable	No immediate threat	None	None	Audible	Audible
II	Threatened					
a	Marginal	Salvageable if promptly treated	Minimal (toe) or none	None	Inaudible	Audible
b	Immediate	Salvageable if immediately revascularized	More than toes, rest pain	Mild/moderate	Inaudible	Audible
III	Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Summarized definitions of categories are as follows: Category I, viable with no immediate limb-threatening condition and audible Doppler signals; category II, threatened limb with marginally (class IIa) or immediately (class IIb) ischemic condition that will result in limb loss if not treated promptly; and category III, profound limb ischemia with imminent tissue loss and permanent neurologic damage that often requires an amputation.
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Table 6. Common Causes of Acute Arterial Ischemia (43)

Embolism	Thrombosis
Atherosclerotic heart disease	Atherosclerosis
Coronary artery disease	Low-flow states
Acute myocardial infarction	Congestive heart failure
Arrhythmia	Hypovolemia
Valvular heart disease	Hypotension
Rheumatic	Hypercoagulable states
Degenerative	Vascular grafts
Congenital	Progression of disease
Bacterial	Intimal hyperplasia
Prosthetic	Mechanical
Artery to artery	Arterial plaque rupture
Aneurysm	Aneurysm
Atherosclerotic plaque	Aortic/arterial dissection
Idiopathic	External compression
Iatrogenic	Iatrogenic
Trauma	Trauma
Paradoxical embolus	
Other	
Air	
Amniotic fluid	
Fat	
Tumor	
Chemicals	
Drugs	

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better served with embolectomy, which can often be performed with local anesthesia. In thrombotic events, the patients often have more gradual onset, and may have a collateral network of arteries and less severe symptoms, all of which may provide enough of a time window to undertake treatment with percutaneous intervention. In cases of embolism, an attempt must be made to discover the source, whether it be a paradoxic embolus, cardiogenic, or valvular, or from a proximal arteriogenic source such as an aneurysm or atherosclerotic plaque. The source of emboli must also be addressed to reduce the likelihood of future embolic events. Doppler imaging examination of the limb should be performed when possible.

Patients with ALI are considered candidates for thrombolysis when they present with Rutherford category 1 or IIa ischemia, and an algorithmic approach has been proposed (**Figure**) (49,56). Patients with category IIb ischemia may be candidates for thrombolysis, but the method of clot removal must be expeditious. Mechanical devices may reduce the time to restoration of flow, thereby allowing patients with more severe degrees of ischemia to undergo percutaneous thrombolysis. The treating physician must make this determination on a case-by-case basis. Patients with category III ischemia should not be treated percutaneously because catheter-based thrombolytic therapy often takes many hours and ischemic changes may become irreversible over the course of treatment. In addition, revascularization of category III ischemia carries the added risk of toxic shock syndrome.

Intravenous heparin at full anticoagulation doses should be initiated as soon as possible and continued until thrombolysis is started. Prompt initiation of anticoagulation reduces or prevents clot propagation and reduces the chances of further embolization. In one study (61), the time from establishing diagnosis to initiation of therapy was correlated with amputation rates. The amputation rates were 6% if thrombolytic therapy was initiated within 12 hours of development of acute symptoms of ischemia, 12% if initiated within 13–24 hours, and 20% if initiated after 24 hours. It is very important to control pain and treat any underlying medical condition such as congestive heart failure and cardiac arrhythmias.

Important questions to consider before undertaking therapy include whether (i) the patient can tolerate the anticipated time of treatment, (ii) the total clot burden is suitable for thrombolysis in a reasonable length of time, (iii) the clot location is within reach of the thrombolytic catheters/devices, and (iv) the patient has risks of thrombolysis/anticoagulation that outweigh the benefits of the thrombolytic therapy.

Published studies (8,45,62) indicate that patients with acute leg ischemia of less than 14 days duration and those with acute bypass graft occlusions benefit most from thrombolysis; the benefits reported were improved survival and improved long-term patency of the limb when thrombolysis was the initial therapeutic option. Subanalysis of the data (8) showed that lower amputation and mortality rates occurred when patients were randomized to undergo thrombolysis versus surgery when symptoms were less than 14 days in duration, whereas a higher rate was seen in patients with symptoms for greater than 14 days. Further analysis of the STILE trial (52) indicated that 1-year amputation-free survival rate was significantly higher in patients with ALI randomized to receive thrombolytic therapy compared with surgery (20% vs 48% [P =.026]; failure of catheter placement occurred in 28% of patients). In a study performed by Ouriel et al (7), in which patients were randomized between surgery and thrombolytic therapy, after 12 months, 84% of the patients randomized to receive thrombolytic therapy were alive, whereas only 58% of those randomized to surgery were still alive (P = .01). Further subgroup analysis of the STILE data in two reports (52,62) suggest that thrombolysis appears to be more effective for graft occlusions than for native artery occlusions. Based on the results of the TOPAS (17) and STILE (8) trials, a working group proposed that thrombolytic therapy should be considered appropriate initial management in patients with acute occlusion of the leg arteries or bypass grafts (48). These recommendations are not absolute, as they are based on subgroup analysis of patient populations within larger trials. Some studies (5,10,11) have also indicated that the likelihood of limb salvage after thrombolytic therapy is greater when a greater number of patent vessels are present.

Contraindications to pharmacologic thrombolytic therapy (**Table 7**) are based on medical conditions thought to increase the risk of local and remote hemorrhage (63). The recommendations were arrived at by consensus and are not evidence-based (48,64,65,66). It may be that risks of remote or systemic hemorrhage are lower with catheter-directed thrombolysis, which uses lower doses of drug compared with systemic doses, albeit over longer periods of time. Therefore, the listed contraindications should be used to weigh the relative risks and benefits of thrombolytic treatment in patients who may have conditions that also increase the risk of the requirement of surgical therapy. Patients with relative contraindications may be appropriate to treat with thrombolysis. When clinically significant bleeding is recognized, continuation of thrombolytic therapy is dependent on the clinical status of the patient and the severity of bleeding. Attempts should be made to identify the site of bleeding and treat the cause appropriately. Contraindications that may exist for catheter-based angiography should also be considered.

Current endovascular therapies employed to treat ALI involve administration of thrombolytic agents through an infusion catheter placed in the thrombus (ie, pharmacologic thrombolysis), mechanical disruption/fragmentation combined with/without aspiration of debris (ie, mechanical thromboembolectomy) or a combination of the techniques (ie, pharmacomechanical thrombolysis). The indication for percutaneous management of ALI is presentation with acute symptoms with Rutherford category 1 or 2 ischemia determined by physical and Doppler examination (**Table 5**) (49,56,57).

Removal of the clot not only restores antegrade blood flow to the distal ischemic limb, but, moreover, it unmasks the underlying causative lesion. Correction of this lesion, whether by endovascular or surgical means, is paramount to good outcome.

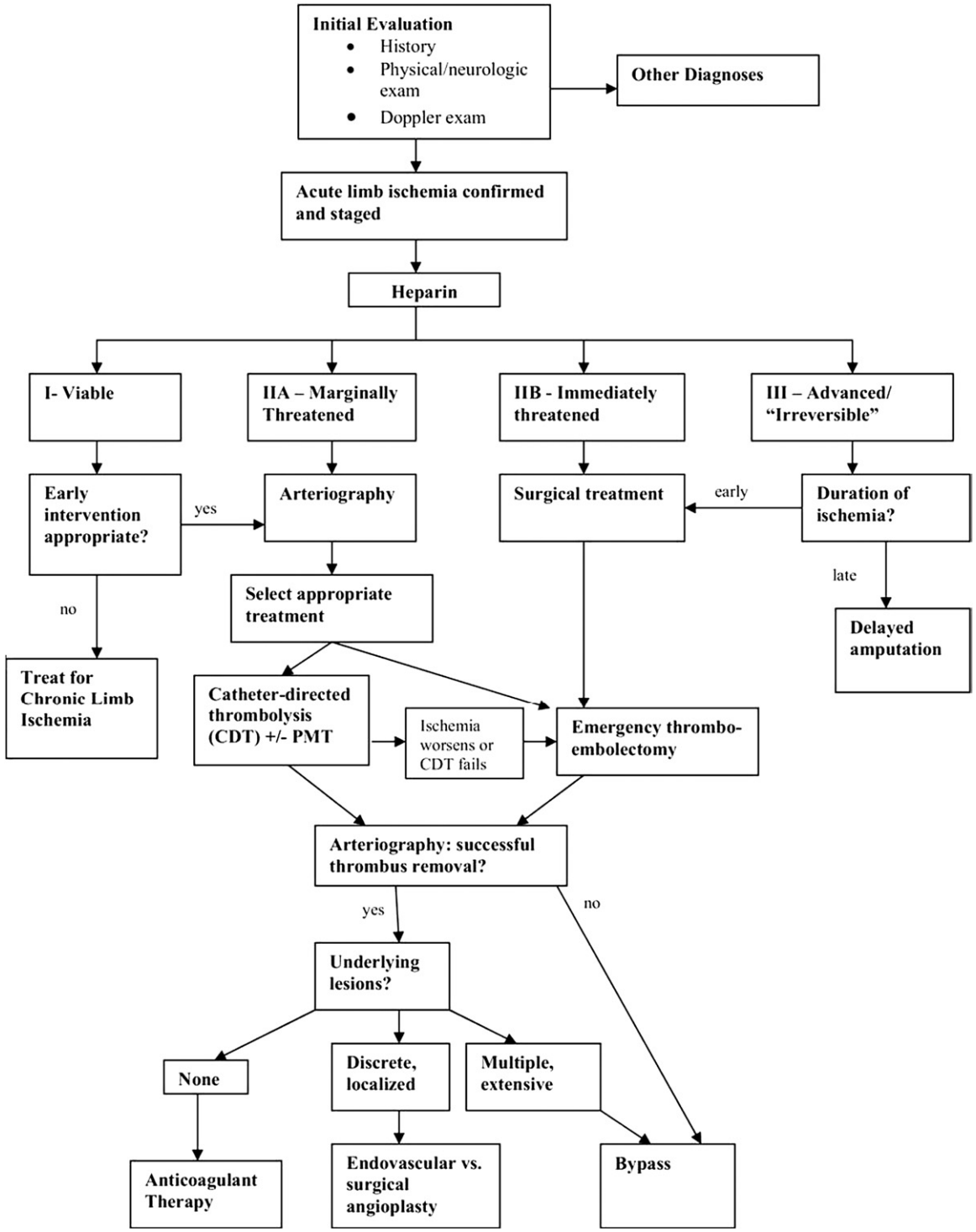

Figure. Proposed algorithm for management of ALI. (Reprinted with permission from Rutherford RB. Clinical staging of acute limb ischemia as the basis for choice of revascularization method: how and when to intervene. Semin Vasc Surg 2009; 22:5–9.)

THROMBOLYTIC THERAPY

Thrombolytic Agents

All clinically available thrombolytic agents are plasminogen activators, and do not directly degrade fibrinogen. They all activate plasminogen, thereby converting plasminogen to plasmin. The plasmin then breaks down the fibrin and fibrinogen contained in the clot into fibrinogen degradation products. All currently available agents have varying degrees of fibrin specificity, the ability to distinguish between circulating and bound plasminogen (**Table 2**). Streptokinase (SK) and urokinase (UK) are non–fibrin-specific plasminogen activators. Tissue plasminogen activators (tPAs) are fibrin-specific agents that preferentially activate fibrin-bound (ie, clot-bound) plasminogen. Their higher fibrin specificity was hoped to lower systemic bleeding complications; however, large trials have shown no significant difference in bleeding rates (48,52,61).

SK is produced by β-hemolytic streptococci with a biphasic half-life: the initial half-life is accounted for by complexing of the molecule with SK antibodies, and the second half-life represents the actual biologic

Table 7. Contraindications to Thrombolytic Therapy

Absolute contraindications
Active clinically significant bleeding
Intracranial hemorrhage
Presence/development of compartment syndrome
Absolute contraindication to anticoagulation
Relative contraindications
Bleeding diathesis
Disseminated intravascular coagulation
Established cerebrovascular event (including transient ischemic attacks) within past 2 mo
Neurosurgery (intracranial, spinal), or intracranial trauma within past 3 mo
Cardiopulmonary resuscitation within past 10 d
Major surgery, or major trauma within past 10 d
Recent eye surgery within past 3 mo
Intracranial tumor, vascular malformation, aneurysm, or seizure disorder
Uncontrolled hypertension (> 180 mm Hg systolic or > 110 mm Hg diastolic blood pressure)
Recent internal hemorrhage, puncture of noncompressible vessel or organ biopsy
Recent major gastrointestinal bleeding within past 10 d
Serious allergic or other reaction to thrombolytic agent, anticoagulant, or contrast media (not controlled by steroid/antihistamine pretreatment)
Severe thrombocytopenia
Pregnancy and immediate postpartum status
Severe liver dysfunction, particularly in cases with coagulopathy
Bacterial endocarditis
Bleeding diathesis
Disseminated intravascular coagulation
Diabetic hemorrhagic retinopathy
Life expectancy of < 1 y

elimination of the protein. SK by itself is not a plasminogen activator; it first must bind to free circulating plasminogen and plasmin to form a complex. This complex in turn converts a second plasminogen molecule to form active plasmin. SK activity is not enhanced in the presence of fibrin. Therefore, it cannot distinguish from fibrin-bound (ie, clot-bound) plasminogen and circulating plasminogen, thereby resulting in a systemic lytic state. As SK is produced by streptococcal bacteria, it often causes allergic reactions (eg, fever, hypotension). SK cannot be safely used a second time within 6 months because it is highly antigenic and results in high levels of antistreptococcal antibodies (67,68). Anistreplase is an anisolated purified SK activator complex, but it is still limited by antigenic effects, and, like SK, it produces a systemic lytic state. Absolute recommendations on drugs and doses are not possible on the basis of available data.

UK is produced in the renal parenchyma, and, unlike SK, is a direct plasminogen activator. UK can be manufactured from purified urine or by tissue culture and recombinant DNA techniques. Abbokinase (Abbott Laboratories, Abbott Park, Illinois) and Kinlytic (Microbix Biosystems, Mississauga, Ontario, Canada) are derived from human neonatal kidney cells grown in tissue culture, and are therefore not antigenic. Recombinant UK (r-UK) is fully glycosalated and derived from a murine hybridoma cell line. It differs from UK by having a higher molecular weight and a shorter half-life. However, despite these differences, r-UK has the same clinical efficacy and safety profile as UK (69). Pro-UK (proUK), a precursor of UK, was discovered in urine in 1979, and subsequently manufactured by recombinant technology by using *Escherichia coli* or mammalian cells. For clinical use, Prolyse (recombinant pro-UK; Abbott Laboratories) was derived from a murine hybridoma cell line by using recombinant technology. It is inactive in plasma and is activated by kallikrein or plasmin to form active two-chain UK. As more plasmin is generated, more pro-UK is converted to active UK. Its fibrin-degrading activity outweighs its fibrinogen-degrading activity. Therefore, it preferentially activates fibrin-bound (ie, clot-bound) plasminogen over free circulating plasminogen. Nonselective activators like SK and UK activate free and bound plasminogen equally and induce systemic plasminemia. A North American multicenter trial comparing three different doses of pro-UK versus UK in 213 patients with lower-extremity arterial occlusion of less than 14 days duration (13) found that, although a higher pro-UK dose resulted in a greater percentage of patients with complete (ie, > 95%) clot lysis at 8 hours, there was a mild increase in bleeding complication rates compared with UK and lower doses of pro-UK. The decrease in serum fibrinogen levels in the patients treated with higher pro-UK doses suggests that fibrin specificity is lost at higher dose regimens. Neither r-UK nor pro-UK are commercially available.

tPA is produced by the endothelial cells lining the blood vessels. Natural tPA is a single-chain (527-amino acid) serine protease with a molecular weight of approximately 65,000 Da. tPAs (eg, alteplase, reteplase, tenecteplase) are fibrin-specific agents that preferentially activate fibrin-bound (ie, clot-bound) plasminogen, which is expressed on the surface of pathologic clots. Alteplase (TPA) was the first recombinant tissue-type plasminogen activator and is identical to native tPA. It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized by using the complementary DNA for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. The manufacturing process involves the secretion of the enzyme alteplase into the culture medium by an established mammalian cell line into which the cDNA for alteplase has been genetically inserted. Alteplase has two advantages over UK and pro-UK: fibrin specificity and fibrin affinity. There have been two prospective, randomized comparisons between UK and TPA reported (8,70). Meyerovtiz et al (70) found a significantly greater systemic fibrinogen degradation in the TPA group, indicating that the fibrin specificity of TPA was lost in their dosing regimen. Although patients treated with TPA showed faster achievement of thrombolysis, there was no difference in the efficacy between the TPA and UK groups. In addition, there was a trend toward higher bleeding complication rates in the TPA group (70). The STILE trial (8) found no significant differences between UK and TPA in any of the outcome variables measured. Swischuk et al (25) and Arepally et al (71) found TPA to have an increased risk of bleeding. Reteplase (RPA) is a second-generation recombinant tissue-type plasminogen activator. It is a synthetic nonglycosylated mutein of tPA consisting of 355 of the 527 amino acids that form tPA (72). The drug is produced in *E. coli* by recombinant DNA techniques. Reteplase does not bind fibrin as tightly as TPA, thereby allowing the drug to diffuse more freely through the clot rather than just binding on the surface of the clot like TPA. At higher concentrations, reteplase does not compete with plasminogen for fibrin-binding sites, allowing plasminogen at the site of the clot to be transformed into clot-dissolving plasmin. These characteristics help explain the faster clot resolution seen with reteplase than with TPA. Multiple small retrospective studies exist but are insufficient to comment on the superior efficacy of this agent (73–75). Tenecteplase (TNK) is a third-generation plasminogen activator with a similar mechanism of action as TPA. It is made of 527-amino acid protein like TPA but differs by six amino acids. This change permits TNK to have a longer half-life, higher fibrin specificity, and improved resistance to plasminogen activator inhibitor compared with TPA. Like TPA, it is also made from recombinant DNA technology by using a mammalian cell line. Razavi et al (76) published a study of 24 patients with peripheral arterial occlusion and 36 patients with deep vein thrombosis in whom TNK was administered by catheter-directed technique at two different doses. They found that TNK doses of 0.25–0.50 mg/h to be safe and effective, with low associated bleeding complication rates (7.3% minor, 1.8% major).

Concomitant use of GIIb/IIIa receptor antagonists for accelerated thrombolysis has shown promising results in small series (29,31,75,77–79) but has yet to be validated in a large study. None of these agents are specifically approved for noncoronary thrombolysis.

Dosage

Urokinase. The most commonly described protocol for UK is a graded infusion regimen consisting of 240,000 U/h for 4 hours, then a lower dosage of 120,000 U/h for a maximum infusion time of 48 hours (1,4,17,80). The TOPAS phase I study (13) appears to show that the dosage of UK associated with the lowest risk of hemorrhage (2%) that maximized thrombolytic efficacy (71%) was 4,000 U/min. No significant differences among dosages and surgery in terms of mortality and amputation were found in this study (13). In a study by Cragg et al (81), a comparison was made between high-dose and low-dose UK infusions for native arterial and graft occlusions. The high-dose UK regimen was 250,000 U/h for 4 hours, then 125,000 U/h. The low-dose UK regimen was 50,000 U/h. This small study suggested that both dose regimens were equally effective but there was a higher frequency of minor bleeding complications in the high-dose group.

Tissue Plasminogen Activators. Alteplase (TPA) weight-adjusted doses have ranged from 0.02 to 0.1 mg/kg/h (82–84), whereas non–weight-based doses generally range from 0.25 to 1.0 mg/h, even though higher doses have been reported (14,15,25,85,86). In general, the lowest effective dose has not been determined. Braithwaite et al (15) performed a multicenter study that randomized 100 patients with acute leg ischemia of less than 30 days duration. This study compared high-dose TPA (3–5-mg bolus doses, then 3.5 mg/h for a maximum of 4 h, then 0.5–1.0 mg/h) versus low-dose TPA (0.5–1.0 mg/h). There were no statistically significant differences between the two groups in terms of 30-day limb salvage or complication rates. An advisory panel was convened in 1999 to provide guidelines for the use of alteplase (66). The suggested dosage regimens were (i) a weight-adjusted dose of 0.001–0.02 mg/kg/h and (ii) a non–weight-adjusted dose of 0.12–2.0 mg/h. No formal recommendation was made regarding the use of weight-adjusted versus non–weight-adjusted dosing (66). The recommended maximum dosing was no greater than 40 mg for catheter-directed therapy.

For reteplase (RPA), a consensus document published in 2001 (87) suggested than the minimum dose should not be less than 0.25 U/h, with a dose range of 0.25–1.0 U/h. Maximum dose amount and infusion time suggested were 20 U and 24 hours, respectively (87). In a study examining different doses of reteplase for lower-extremity arterial occlusions (28), doses of 0.5 U/h, 0.25 U/h, and 0.125 U/h were found to be equally effective, with more bleeding complications with the highest dose.

Delivery Methods

Intravenous administration of thrombolytic agents should not be performed for ALI. A randomized parallel-group study (50) showed that intravenous administration of TPA led to a higher rate of hemorrhagic complications with less successful thrombolysis than intraarterial delivery.

Treatment is usually initiated when the occluded segment is successfully traversed with a guide wire (ie, guide wire traversal test), a concept introduced by McNamara and Fischer (1). Attempts to pass a guide wire through the acute thrombus to initiate thrombolysis should be made. If a wire cannot be passed, a short period of thrombolysis may be initiated. If a wire cannot be passed after this short period of time, consideration should be given to other methods of revascularization.

Multiple techniques for intrathrombus infusion of thrombolytic agents have been described, including (i) intrathrombus bolus administration followed by continuous low-dose intrathrombus infusion with use of an infusion wire or catheter with multiple side holes for maximum surface area exposure (88,89); (ii) stepwise and graded intrathrombus infusion; and (iii) pulse-spray pharmacomechanical thrombolysis (90–92). Intrathrombus infusion represents the current state of practice, with placement of an infusion wire or multiple–side hole delivery catheter completely along the length of the thrombus, as this is associated with a greater chance of complete thrombolysis (45).

Intrathrombus bolus administration of TPA appears to reduce the duration of treatment and may be of advantage in acutely ischemic limbs, but with increased risk of hemorrhage compared with lower-dose continuous infusion. In a study by Braithwaite et al (15), the median duration of infusion was decreased by 80% from 20 hours to 4 hours, with almost 50% of patients exhibiting complete or clinically useful thrombolysis by 4 hours. When bolus technique was compared with continuous infusion in a study by Ward et al (93), a 46% decrease in infusion time was observed, but with a greater incidence of major hemorrhage. Another prospective, randomized study comparing high-dose bolus TPA plus infusion versus infusion without a bolus dose (94) supports this approach.

Although intraoperative thrombolysis may have a role at the time of operative revascularization to dissolve clot in the distal vasculature, sufficient data are not available to allow an opinion regarding efficacy and outcome to be rendered. In a single study with 53 patients treated with the intraoperative technique (95), limb salvage was obtained in 70% of cases.

Ultrasound (US)-enhanced thrombolysis is one of the newest ideas in thrombolysis, which uses sound waves to accelerate thrombolysis. Low-frequency US mechanically fragments clots and augments enzymatic fibrinolysis (96–98). In vitro studies (97,99–101) have shown accelerated clot lysis by loosening fibrin strands, increasing thrombus permeability, and exposing more plasminogen receptors for binding. Several devices have been developed to try to increase the efficacy of clot dissolution by using these principles, and the Ekosonic Mach-4e device (Ekos, Bothell, Washington) is currently commercially available. In addition to drug delivery, the Ekosonic device delivers sound waves into the clot in the aim to accelerate the speed and improve the completeness of thrombolysis (102,103). A Dutch randomized trial comparing standard catheter-directed thrombolysis versus US-accelerated thrombolysis for thromboembolic infrainguinal disease (104) is currently under way.

The delivery method or device that provides optimal thrombolysis has not been studied in large prospective trials.

Heparin Use during Thrombolytic Infusions

The published literature shows varying doses used in thrombolytic infusion, from none to therapeutic anticoagulation, with no dose identified that predicts adverse bleeding. Heparin should be used carefully during thrombolytic infusions because of the risk of bleeding. Generally, subtherapeutic doses of heparin are acceptable when used in combination with thrombolytic therapy, although therapeutic doses are recommended with UK infusion treatment. In the study by McNamara and Fischer (1), pericatheter thrombosis occurred in two of seven infusions when heparin was not administered concurrently. In a study by Ouriel et al (17), therapeutic doses of heparin initially administered intravenously were associated with an intracranial hemorrhage rate of 4.8%. The protocol in this study (17) was subsequently revised by reducing the heparin dose to prevent pericatheter thrombosis to a subtherapeutic dose and administering it through the arterial sheath instead of intravenously.

With fibrinogenolysis, the products of fibrinogen degradation increase the patient's sensitivity to heparin, possibly making the patient more prone to bleeding. Careful monitoring of partial thromboplastin time is recommended. Postthrombolysis anticoagulation is recommended until the underlying lesion, if any, is corrected.

Laboratory Monitoring

No clinical trials have been completed to support laboratory monitoring that may predict adverse bleeding during thrombolytic therapy. Although monitoring of serum fibrinogen levels is thought by some to predict adverse bleeding, no pivotal study has validated this belief. In the Prourokinase versus Recanalization of Peripheral Occlusions, Safety and Efficacy trial by Ouriel et al (20), 13 of 16 patients (81.3%) with a serum fibrinogen level of less than 100 mg/dL had a major or minor bleeding complication, compared with 105 of 179 patients (58.7%) with serum

fibrinogen levels greater than 100 mg/dL ($P = .108$). In the STILE trial (8), it was demonstrated that patients with bleeding complications had a significantly lower plasma fibrinogen level at the end of infusion ($P = .01$). Another study (79) demonstrated that major complications were associated with a mean 72% decrease in fibrinogen level, whereas minor complications were associated with a mean 46% decrease in fibrinogen level. Routine monitoring of hemoglobin may allow for detection of significant occult bleeding before it becomes clinically apparent.

The tPAs (TPA, RPA, and, to a lesser extent, TNK) generate fragment X, a high molecular weight fibrinogen degradation product. When fragment X is incorporated into the clot, the clot becomes more susceptible to lysis. However, fragment X also becomes incorporated into hemostatic plugs, making them more easily lysed and thereby increasing the potential for bleeding. In contrast to tPAs, UK and SK, which are not fibrin-specific, do not generate fragment X. Instead, they generate much smaller fibrinogen degradation products (fragments Y, D, and E) that are neither clottable nor incorporated into the hemostatic plug.

Adjunctive Techniques

The complexity of the underlying causative lesion that is unmasked through thrombolytic therapy predicts the long-term patency and limb salvage rates. Hanover et al (39) found that patients who require thrombolytic therapy only (with no adjunctive endovascular or surgical treatment required) had much higher primary patency rates (95.2% at 1 mo, 88.4% at 6 mo and 1 y) and limb salvage rates (100% at 1 mo, 6 mo, and 1 y) compared with those who required adjunctive endovascular or open surgical treatments or a combination of the two.

When flow in the vessel has been restored, repeat angiography should be performed to define the vascular anatomy and areas of disease that may require additional treatment. In most cases, a causative lesion will be identified, and this should be managed with the appropriate endovascular technique or conventional surgical procedure. Failure to detect and rectify an underlying lesion is associated with poor long-term patency.

The speed and long-term efficacy of intraarterial thrombolysis can be enhanced by using adjunctive techniques. These techniques will help achieve two clinically important endpoints:

1. They may be used in conjunction with thrombolysis to remove insoluble material, or debulk the thrombus to accelerate the restoration of flow; and
2. They may be used to correct underlying lesions at the time of thrombolysis or in the periprocedural period.

Among the procedures that may be used in conjunction with or independent of pharmacologic thrombolysis are percutaneous aspiration thromboembolectomy (PAT) and the use of mechanical thromboembolectomy devices (MTDs). In patients in whom it is important to accelerate thrombolysis or remove residual clot, PAT and MTD use are alternatives.

Percutaneous Aspiration Thromboembolectomy

The PAT technique uses a large-bore catheter connected to a syringe to aspirate (ie, suction) clot from vessels. This technique, first described by Sniderman et al (105), can be used alone or in conjunction with thrombolytic therapy. In a retrospective study of 102 patients with acute arterial embolic occlusions (106), primary angiographic success, defined as reperfusion in a previously completely occluded vascular segment, was obtained in 87.3% of cases; however, thrombolytic drug was used in as many as 60% of cases. In another study in patients who had only acute embolic occlusions (107), PAT was successful in 77 of 90 limbs (86%); however, UK limited to 200,000 U was required in 74 cases. In another study (108), PAT alone was successful in 31% of cases of acute and subacute arterial occlusion. Analysis of cases that were successful showed that all were the result of embolic occlusion (108). PAT is typically used as an adjunct to thrombolysis in acute arterial occlusion, or can be used as salvage therapy to remove distal emboli. Low-profile, dual-lumen, rapid-exchange aspiration thrombectomy catheters are also commercially available, such as the Pronto extraction catheter (Vascular Solutions, Minneapolis, Minnesota), Export catheter (Medtronic, Minneapolis, Minnesota), Xpress-Way extraction catheter (Atrium Medical), ASAP catheter (Merit Medical, South Jordan, Utah), and Fetch catheter (Medrad). The efficacy and volume of clot extracted with these catheters are not equivalent to those extracted with the use of MTDs. However, the apparent benefits of these catheters are their atraumatic distal tips, minimal risk of distal embolization, ability to intervene within smaller-caliber arteries, and no evidence of hemolysis. Data on ALI with these devices are very limited, and there are no comparative data between PAT catheters and MTDs.

Percutaneous Mechanical Thromboembolectomy Device

As many as 20% of patients can have a contraindication to thrombolytic therapy (8). MTDs are particularly useful in such patients with contraindications to thrombolytic therapy. In patients at higher risk for bleeding, MTDs can be used to debulk the thrombus mass before local lysis to shorten the lytic treatment period, thereby limiting the dose of thrombolytic agent needed. MTDs may also be used as an adjunctive procedure for incomplete thrombolysis or to treat distal embolic complication of catheter-directed thrombolysis.

MTDs can be categorized into (i) mechanical thrombectomy devices that mechanically disrupt thrombus along with aspirating the debris and (ii) hydrodynamic devices that rely on aspiration as well as a Venturi effect of infused saline solution or other pharmacologic agent injected under pressure. Basic principles for use of these devices are to minimize endothelial damage and downstream embolization. Many of these catheter devices allow concurrent pulse-spray administration of a thrombolytic agent. This technology has the potential to minimize the two main drawbacks of endovascular ALI therapy: the long duration of thrombolytic infusion that is needed to establish full arterial perfusion and hemorrhagic complications.

A multicenter registry of 99 patients with limb ischemia treated with the AngioJet rheolytic thrombectomy device (Medrad) reported 70% substantial or complete revascularization (ie, < 50% residual defect) and in-hospital and 30-day mortality rates of less than 5% (37). Primary patency rates of 74% and 69% have been reported at 3 months and 1 year, respectively (107). MTD complications include hemolysis and possible renal failure secondary to release of free hemoglobin. Hemolysis and fluid overload are possible with these devices. With the AngioJet device, the manufacturer recommends that the pump should be run less than 10 minutes in a flowing blood field to prevent excessive hemolysis. Also, use of the AngioJet device close to the heart may result in bradyarrhythmias (ie, mild bradycardia to asystole) as a result of adenosine release caused by cell lysis (109). The current commercially available MTDs for ALI—the AngioJet (Medrad), Jetstream (Pathway Medical, Kirkland, Washington), and Rinspirator (ev3, Plymouth, Minnesota) devices—are all plagued with large particulate debris and distal embolization (110).

Isolated pharmacomechanical thrombolysis may help to minimize or possibly eliminate the risk of embolization. The Trellis-6 peripheral infusion system (Covidien) uses balloons that are inflated, one proximal to the thrombus and the other distal to the thrombus. Between the balloons are infusion holes through which the thrombolytic agent is introduced, limiting systemic dispersion. Then, mechanical dispersion of the thrombolytic agent with maceration of the clot is accomplished by oscillation of the catheter by a powered sinusoidal wire. Then, the dissolved clot is aspirated through the catheter (111–114).

Well organized emboli are still problematic for most MTD devices. Use of MTDs may reduce the thrombus mass, thereby reducing the length of time of catheter-directed thrombolysis and the total dose of thrombolytic drug needed to achieve clinical success, possibly decreasing hemorrhagic complications and improving outcome. However, experience with MTDs is limited (115–119). Limited population sizes in multiple retrospective studies with different definitions of success and outcomes limits critical analysis. Comparative randomized studies are needed to determine if MTDs are faster and safer, and how effective they are compared with pharmacologic thrombolysis. A few nonrandomized

studies document higher amputation-free success rates associated with initial endovascular MTD procedures, with low repeat intervention rates (40). MTDs may serve a role in removal of clot in patients with category IIb acute ischemia within 2 hours of presentation of symptoms (56,57). A recommendation based on current literature for use of MTDs as a stand-alone method for thrombolysis cannot be made.

SUCCESS RATES

Technical Success

Technical success is defined as restoration of antegrade flow with relief of the acute ischemic symptoms at rest. The suggested threshold value for technical success was supported by the weight of literature evidence and panel consensus (**Appendix C**).

Overall Clinical Success

Overall clinical success is defined as relief of the acute ischemic symptoms and return of the patient to at least his/her preocclusive clinical baseline level after the removal of thrombus and performance of adjunctive procedures. The suggested threshold value for overall clinical success was supported by 80% panel consensus with use of the modified Delphi technique (**Appendix C**).

COMPLICATIONS

Published rates for individual types of complications are highly dependent on patient selection and are based on series comprising several hundred patients, which is a volume larger than most individual practitioners are likely to treat. Generally, the complication-specific thresholds should be set higher than the complication-specific reported rates listed herein. It is also recognized that a single complication can cause a rate to cross above a complication-specific threshold when the complication occurs within a small patient volume, (eg, early in a quality improvement program). In this situation, the overall procedure threshold is more appropriate for use in a quality improvement program. The reported complications and suggested threshold values were supported by the weight of literature evidence and panel consensus (**Appendix C**).

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APPENDIX A: CONSENSUS METHODOLOGY

Reported complication-specific rates in some cases reflect the aggregate of major and minor complications. Thresholds are derived from critical evaluation of the literature, evaluation of empirical data from Standards of Practice Committee members' practices, and, when available, the SIR HI-IQ System national database.

Consensus on statements in this document was obtained with use of a modified Delphi technique (41).

APPENDIX B: CLASSIFICATION OF COMPLICATIONS BY OUTCOME

Minor Complications

A. No therapy, no consequence.

B. Nominal therapy, no consequence; includes overnight admission for observation only.

Minor Complications

C. Require therapy, minor hospitalization ($<$ 48 h).

D. Require major therapy, unplanned increase in level of care, prolonged hospitalization ($>$ 48 h).

E. Permanent adverse sequelae.

F. Death.

Appendix C . Suggested Thresholds

Outcome	Threshold (%)	
Indications for percutaneous management of ALI	99	
Technical success	70	
Overall clinical success	75	
Specific Major Complications for Thrombolysis of ALI	**Reported Rate (%)**	**Suggested Threshold (%)**
Pharmacologic		
Intracranial hemorrhage	0–2.5	2
Major bleed requiring transfusion and/or surgery	1–20	10
Compartment syndrome	1–10	4*
Distal embolization not corrected with thrombolysis	1–5	5
Mechanical		
Distal embolization (mechanical thrombectomy/aspiration)	1.8	2

* This value was determined based on the weight of the majority of studies presented in the evidence table excluding a single study in which the observed complication rate was 9.8%.