

TABLE 43.2 Pharmacology of US Food and Drug Administration – Approved Thrombolytic Agents

Name	Molecular Weight (kD)	Half-Life (Min)	Fibrin Specificity	Mechanism of Action	Cost (\$US) ^a
Streptokinase	47	20	0	Plasminogen activator	NA
Urokinase	33	13	++	Plasminogen activator	NA
Alteplase	70	5	+++	Recombinant human tissue plasminogen activator	\$40/mg
Reteplase	39	15	++	Same as alteplase but has extended half-life because of lack of carbohydrate side chains, finger domain, epidermal growth factor, and kringle 1 domain	\$150/U
Tenecteplase	65	22	++++	Same as alteplase but has three single-amino acid and a tetra-alanine substitution, which extends its half-life	\$70/mg

^aCosts for thrombolytic agents vary depending on location and individual pricing agreements. These costs are from a tertiary hospital based in the Los Angeles, California, region. NA, no longer manufactured in the United States.

THROMBOLYTIC AGENTS

Currently, the most commonly used thrombolytic agents are the recombinant plasminogen activators and genetically modified variants (Table 43.1); however, a number of other investigational thrombolytic agents are being studied. Characteristics of commercially available thrombolytic agents are listed in Table 43.2. Thrombolytic agents can be classified as follows:

1. Plasminogen activators: The mechanism of action for thrombolysis is indirect. These agents convert intrinsic plasminogen to active plasmin that cleaves linked fibrin. There are two types:
 - a. Biologic, naturally occurring (e.g., SK and UK)
 - b. Recombinant and genetically modified variants (e.g., alteplase, reteplase, tenecteplase)
2. Direct-acting agents: The mechanism of action is by direct cleavage of fibrin linked strands.

Biologic, Naturally Occurring Plasminogen Activators

Streptokinase

SK is FDA approved for use in most clinical applications: AMI, PE, DVT, peripheral arterial thrombosis, or embolism (Table 43.1). It has been marketed under different names – Kabikinase (Pharmacia & Upjohn, Somerset County, NJ) and Strep-tase (CSL Behring, King of Prussia, PA) – but in 2004, CSL Behring (the only manufacturer of SK in the United States) discontinued production. Despite its multiple FDA indications, it is rarely used in the United States because of its associated side effects. In developing countries, SK is still used because of its low cost. There are now recombinant technologies to produce SK via *Escherichia coli*, but these products can have variable lytic activity.^{41–43}

SK is a 414-amino acid, single-chain protein with a molecular weight of 47 kD. Produced by β -hemolytic streptococci, it is present in the broth of the cultured bacteria, allowing for ease of purification and isolation. After multiple strains of streptococci were tested, the Lancefield group C *Streptococcus equisimilis* was chosen for pharmaceutical production because

it lacks production of the erythrogenic toxin and has fastidious growth requirements.⁴⁴

SK has three main structural domains: α , β , and γ . The β domain is involved in the SK-plasminogen complex formation, and the γ domain assists in making the plasminogen within this complex active.⁴⁵ The SK-plasminogen complex has a half-life of 20 minutes and does not dissociate.^{1,46} It can be inactivated by systemic plasmin inhibitors (α_2 -antiplasmin and α_2 -macroglobulin), but when administered as a therapeutic agent, concentrations are increased such that the SK-plasminogen complex overwhelms this inhibition.⁴⁷

Because SK is derived from streptococci, previous bacterial infection or exposure to SK can cause antibody formation, which makes subsequent SK doses inactive. SK-neutralizing antibodies last for a minimum of 4 days and can persist for up to 4 years in 50% of patients.^{48,49} Minor hypersensitivity reactions to SK after readministration are uncommon, 4.4% in one study,⁵⁰ but cases of life-threatening anaphylaxis and serum sickness have been documented.^{51,52} Readministration of SK can be attempted up to 4 days after the initial dose; however, repeat dosing after 5 days to a year is not recommended due to inactivation by an increased amount of antistreptococcal antibodies.¹

Urokinase

Unlike SK, UK lacks antigenicity because it is normally present at low levels in human plasma (10 μ g/L).⁵³ It is called urine plasminogen activator (u-PA) when found *in vivo* and is normally involved in intracellular signalling pathways and cell proliferation, adhesion, and migration.^{54,55} Produced predominantly by kidney cells, commercially used UK was originally isolated from urine.

Native, or naturally occurring, UK exists in a number of forms in both plasma and urine. The precursor to all forms is prourokinase, a 55-kD, 411-amino acid, single-chain protein also called single-chain urokinase plasminogen activator (scu-PA). It has little enzymatic activity, but in the presence of fibrin UK is cleaved by plasmin into active forms.^{56,57} The resultant high-molecular-weight UK is the predominant form found in urine and is also called a two-chain UK plasminogen activator. It weighs 55 kD and is composed of a 22-kD light chain and a 33-kD heavy chain linked by a single disulfide bond.⁵⁸ The

final form is the 33-kD, low-molecular-weight UK, which is an enzymatically degraded form of high-molecular-weight UK.⁵⁹

Despite the poor fibrin/fibrinogen affinity of naturally occurring UK, it was previously the only alternative to SK. UK was originally marketed as Abbokinase (Abbott, Abbott Park, IL). It is rapidly cleared by the liver, and its half-life is 6.4 to 18.8 minutes, with a volume of distribution of 11.5 L.⁵ Current methods of production use donated human kidney cells from neonates who have died from noninfectious causes. The neonatal kidney cells can be cultured to secrete large quantities of UK.^{5,60}

The trade name Abbokinase was stigmatized after the FDA halted its production in 1999 due to manufacturing issues and viral validation.⁶¹ The FDA intervention created a relative shortage of UK and led to investigational development of other thrombolytic agents such as modified SK, rt-PA, and staphylokinase. In 2002, Abbokinase was reintroduced by Abbott Laboratories. In 2006, Abbokinase was sold to ImaRx, and a year later its trade name was changed to Kinlytic. Two years later, in September 2008, Microbix Biosystems (Ontario, Canada) acquired all the rights related to UK from ImaRx.⁶² Of note, the only licensed indication for UK is PE (Table 43.1), but before being taken off the market in 1999, UK was FDA approved for PE, AMI, and catheter occlusion.

Recombinant Plasminogen Activators

Recombinant Urokinase

To improve the yield of manufactured UK, investigators have produced recombinant UK from genetically engineered mouse hybridoma cells. Recombinant UK, or urokinase alfa, is a 48-kD, two-chain UK once marketed as Open-Cath-R (ImaRx).

Despite successful clinical trials in treating catheter occlusion, it is not currently available in the United States.^{63,64}

Alteplase

Currently alteplase, or rt-PA, is the most commonly used thrombolytic agent in clinical practice. It is identical to the naturally occurring t-PA, which is normally produced by endothelial cells. After sequencing of the native t-PA protein, recombinant technology now produces rt-PA from Chinese hamster ovary cells.² rt-PA and t-PA have the same molecular structure and characteristics (Fig. 43.2). Both are 70-kD molecules and contain five distinct functional domains. The carboxyl-terminal protease domain cleaves the plasminogen peptide bond, arginine 560–valine 561, which converts plasminogen to plasmin.⁶⁵ The fibronectin finger domain and the two kringle domains assist in binding to fibrin. Kringle domains are triple-looped, disulfide-bonded structures of about 80 amino acid residues that contain lysine-binding sites with different affinities for various molecules and receptors.⁶⁶ The epidermal growth factor (EGF) domain assists in liver binding and clearance and gives rt-PA a short half-life of 5 minutes and a terminal half-life of 72 minutes.² Since rt-PA is the same protein as native t-PA, it typically lacks antigenicity, but rare cases of hypersensitivity and allergic reactions have been reported.^{67,68}

Alteplase was developed jointly by Genentech in the United States and Boehringer Ingelheim in Germany. It is marketed in the United States as Activase and Cathflo (Genentech, Inc., South San Francisco, CA) and in Europe as Actilyse (Boehringer Ingelheim, Ingelheim, Germany). Activase has FDA approval for use in patients with AMI, PE, and AIS, whereas Cathflo

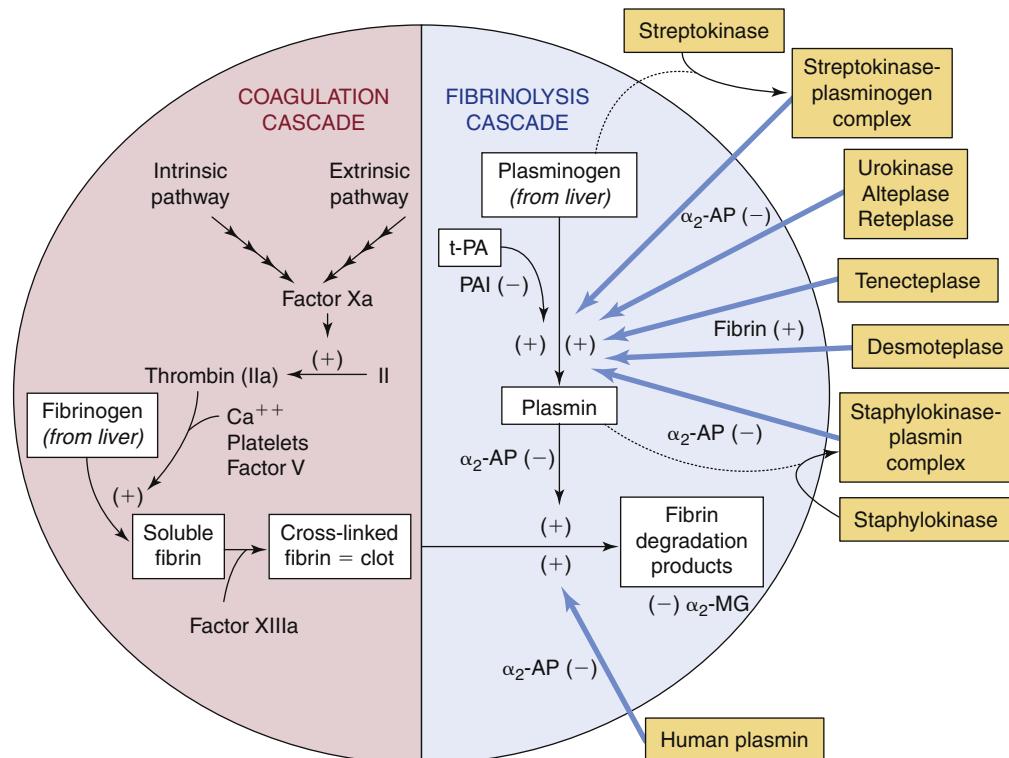


Figure 43.2 Coagulation and fibrinolytic pathway in relation to thrombolytic agents and the mechanism of action. α_2 -MG, α_2 -Macroglobulin; α_2 -AP, α_2 -antiplasmin; PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator.

(which is alteplase packaged into 2-mg vials) is approved for occluded central venous catheters (Table 43.1).

Reteplase

Removal of the finger, EGF, and kringle K1 domains of rt-PA results in a protein called reteplase (Fig. 43.3 and Table 43.2). This 355-amino acid protein also lacks carbohydrate side chains because it is produced from *E. coli* rather than from mammalian cells.⁶⁹ These modifications remove the less desirable characteristics of native t-PA. Lack of the EGF and carbohydrate side chains decreases liver clearance and thus prolongs its half-life to 15 minutes and terminal half-life to 1.6 hours. This allows bolus dosing of reteplase, usually in two separate 10-unit intravenous doses 30 minutes apart.^{70,71} Reteplase is cleared by both the renal and hepatic systems. Although reteplase lacks the EGF and K1 domains, retention of the K2 domain still gives it some fibrin/fibrinogen specificity.

Reteplase was originally developed by Boehringer Ingelheim, which merged with Roche. Abroad, reteplase was

marketed as Rapilysin (Roche, Basel, Switzerland), but in the United States it was marketed as Retavase (EKR Therapeutics, Cedar Knolls, NJ). The rights to Retavase in the United States have gone from Roche to Centocor (Horsham, PA), to PDL, Inc. (Redwood City, CA), in 2006, to EKR Therapeutics in 2008, and since June 2012 to Cornerstone Therapeutics (Cary, NC). It is FDA approved for AMI (Table 43.1).

Tenecteplase

Tenecteplase is another genetically modified rt-PA produced in Chinese hamster ovary cells. It differs from native t-PA in three ways: threonine 103 is replaced by asparagine; asparagine 117 is replaced by glutamine (both within the K1 domain); and the amino acid sequence from positions 296 to 299 within the carboxyl-protease domain is replaced by four alanines (Fig. 43.3).⁴ The tetra-alanine substitution creates increased fibrin specificity (Fig. 43.2). The substitution at position 103 allows decreased clearance, and the position 117 exchange is needed to retain the thrombolytic effect of the entire protein (Table 43.2).^{71,72}

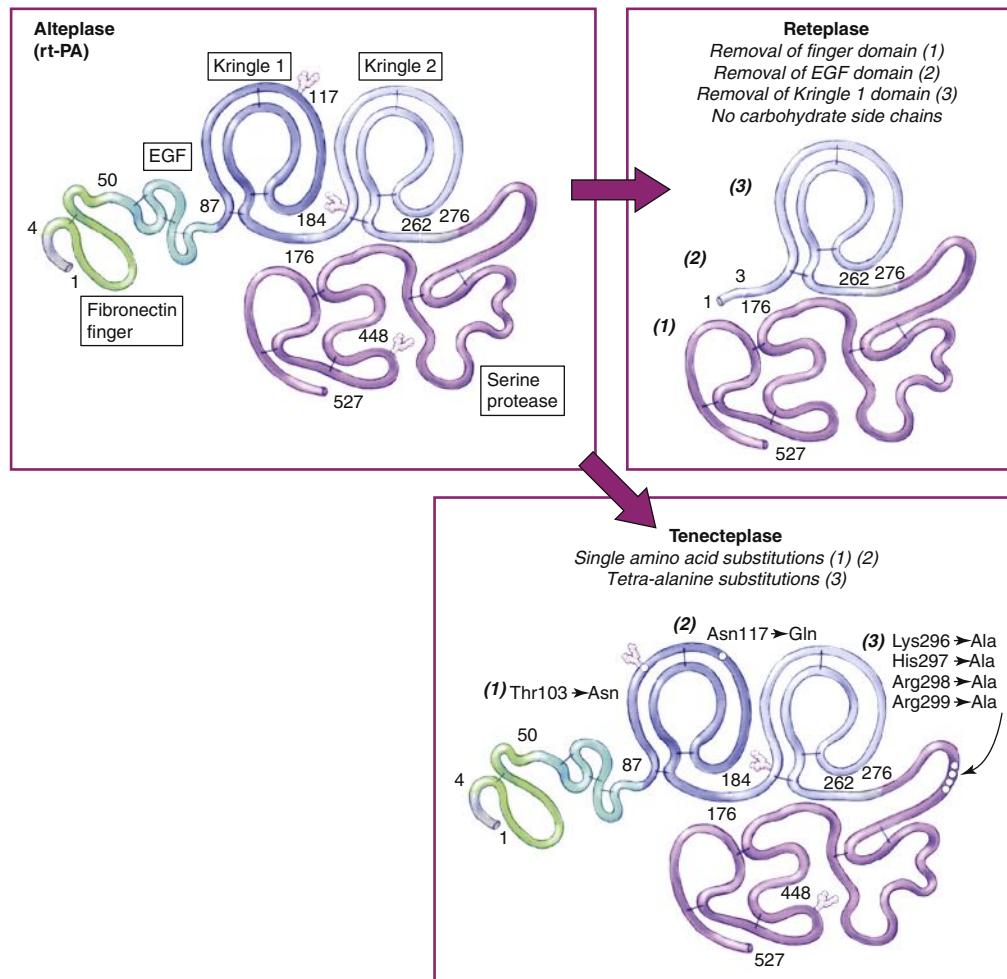


Figure 43.3 Molecular Structure of the Recombinant Plasminogen Activators. EGF, epidermal growth factor. (Image modified, with permission, from Fig. 41.2 in Llevadot J, Giugliano RP, Antman E. Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA*. 2001;286:442–449. Copyright © 2001, American Medical Association. All rights reserved.)

These modifications give tenecteplase a longer half-life than rt-PA, while retaining fibrin affinity. *In vivo* models demonstrate an 80-fold higher resistance to plasminogen activator inhibitor-1 (PAI-1) and 14-fold enhanced fibrin specificity when compared with rt-PA.⁷² Tenecteplase half-life is 20 to 24 minutes, with a terminal-phase half-life of 90 to 130 minutes, and primarily hepatic clearance. Dosing is based on patient weight and administered as a single bolus.⁴ In 2000, tenecteplase was approved by the FDA for AMI and marketed as TNKase (Genentech; Table 43.1). Abroad, tenecteplase is known as Metalyse (Boehringer Ingelheim).

Direct-Acting Agents

All the thrombolytic agents described above are plasminogen activators that convert intrinsic plasminogen to active plasmin, which cleaves linked fibrin. This “indirect” method of achieving thrombolysis results in a varied thrombolytic response. Direct-acting thrombolytic agents could theoretically eliminate this variability, since they act directly on the fibrin polymer. However, these “plasmin”-like compounds are inhibited by circulating inactivators and therefore cannot be delivered systemically. Thus catheter-directed administration of these agents to the offending thrombus is required for therapeutic effect.

Plasmin

The only direct-acting thrombolytic currently under investigation is plasmin. As early as 1960, human plasmin was investigated to treat thrombotic occlusion, but the initial clinical results were poor because of inactivation of systemically administered plasmin by α_2 -antiplasmin.^{73,74} Still, later animal studies demonstrated that plasmin directly delivered to the thrombus provided more rapid and effective thrombolysis than currently available plasminogen activators.⁷⁵

Talecris (Barcelona, Spain), purchased by Grifols in 2011, is investigating two forms of plasmin. The first form is γ -Plasmin (TAL-6003), a recombinant, truncated plasmin that is expressed by *Escherichia coli* in its inactive form (recombinant plasminogen).⁷⁶ It is a simplified form of human plasmin, in which the K1 domain is directly attached to the serine protease domain. This modified plasmin has the potential for increased activity and fibrin specificity, with high potency and efficacy.^{77,78}

The other form is human plasmin. It is obtained from donors who are screened to rule out blood-borne pathogens. Phase I and II clinical trials in the Plasmin Revascularization by Intra-thrombus Infusion for the Ischemic Lower Extremity (PRIORITY) study tested a total dose of plasmin from 25 to 175 mg, in 25-mg increments. Using CDT and pulse-spray delivery, 27% was given as a bolus; then 30 minutes later another 13% of the total dose was given as a second bolus, and the last 60% was infused over a period of 4.5 hours. Thrombus resolution ($\geq 50\%$) occurred in 79% of subjects receiving 125 to 175 mg of plasmin, as compared with 50% who received 25 to 100 mg, with no trend toward more bleeding at higher doses of plasmin. Major bleeding occurred in 4.8%, and minor bleeding in 15.7%.⁷⁹

A phase II randomized trial comparing plasmin with placebo and rt-PA in acute peripheral artery occlusion suggested a

potential benefit in plasmin (150 or 250 mg) over rt-PA; however, no specific benefit was seen with increasing the plasmin dose from 150 to 250 mg. This trial demonstrated a lower risk of bleeding events and drug-related adverse events in the plasmin group, but indicated that the optimal delivery method and infusion rate warrants further studies.^{80,81} Phase I/IIa trials of CDT using plasmin (doses of 20, 40, 80 mg) in AIS within a 9-hour window enrolled 40 patients and found that only 25% achieved successful recanalization. While suboptimal plasmin delivery was suspected, there was a suggestion that slower infusion rates could increase lytic efficacy.^{82,83}

CLINICAL APPLICATIONS

Each thrombolytic agent has been studied in a number of well-performed multicenter, randomized clinical trials, and although the FDA-licensed indications are limited for most agents, off-label use is common. The choice of agent is often based on the treating physician’s experience and medication availability in the hospital. In most facilities, rt-PA is the most readily available, followed by reteplase and tenecteplase.

Acute Myocardial Infarction

In most centers, emergency cardiac catheterization has replaced thrombolytic treatment of AMI, but in institutions without this capability, IVT still has a role. Furthermore, the development and dosing of almost every new thrombolytic agent has been tested in patients with AMI. The first trial to establish IVT as a useful treatment of AMI was reported in 1986 (Fig. 43.1). The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) study randomized 11,806 patients seen within 12 hours of the onset of symptoms to receive intravenous SK or placebo. At 21 days, overall hospital mortality was 10.7% in SK recipients versus 13% in controls ($P = 0.0002$).⁸⁴ The International Study of Infarct Survival (ISIS) 2 not only confirmed the benefits of SK versus placebo in patients with AMI but also demonstrated combination therapy with aspirin to be beneficial.⁵⁰

Similarly, the use of rt-PA for AMI has been extensively studied. The results of the Anglo-Scandinavian Study of Early Thrombosis (ASSET) demonstrated the superiority of rt-PA over placebo in 5011 randomized patients with AMI.⁸⁵ In comparing rt-PA with SK, several trials have demonstrated superiority of rt-PA over SK in respect to coronary arterial flow⁸⁶ and relative risk of 30-day mortality.^{86–88} Furthermore, reteplase and tenecteplase have been studied in a number of trials that ultimately established a licensed indication for AMI (Table 43.3).^{89–95}

Pulmonary Embolism

Multiple trials with different thrombolytic agents in various dosages to treat PE have been completed. Unlike AMI, IVT for the management of PE has not consistently demonstrated mortality benefits. Success thus far has been based on improved pulmonary angiography, lung scans, or pulmonary pressure (or any combination of these endpoints).^{96–103} Current thrombolytic agents with FDA approval to treat PE include alteplase

TABLE 43.3**Dosing of Currently Available Thrombolytic Agents for Acute Myocardial Infarction**

Agent	Dose
Alteplase	100 mg in accelerated or 3-h infusion: Accelerated infusion: Give 15-mg bolus, then 50 mg over next 30-min period, then 35 mg over next 60-min period 3-h infusion: Give 60 mg during first hour (of which 6–10 mg is administered as a bolus), then 20 mg during the second hour, then 20 mg during the third hour
Reteplase	10 U + 10 U double-bolus injection, each 10 U over 2-min period, 30 min apart
Tenecteplase	Weight-based dosing, single bolus (30–50 mg) over 5-s period, not to exceed 50 mg

Dosages are for adult use (≈ 70 kg) and intravenous injection.

and reteplase (Table 43.4) (see Ch. 152, Pulmonary Embolism: Presentation, Natural History, and Treatment).

In 2016, the Tenth American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy did not support the routine use of IVT for acute PE (grade 1B) unless the patient was hemodynamically unstable or becoming unstable despite anticoagulation (grade 2B). IVT with the shortest infusion times are still recommended over CDT. However, whereas previously the ACCP recommended against CDT all together, they now weakly recommend CDT (in combination with mechanical thrombectomy) in patients with an acute PE that is associated with hypotension and either contraindications to IVT, failed IVT, or shock that is likely to cause death before IVT can take effect.²⁵

These ACCP recommendations are supported by evidence demonstrating that mechanical device-assisted thrombolysis improves thrombus removal with a smaller dose of thrombolytic agent.^{104,105} One such device, the Ekosonic Endovascular System (EKOS, Bothell, WA), when used to assist thrombolysis has demonstrated the capacity to rapidly clear thrombus in patients with large pulmonary thrombi.^{105,106} The ULTrasound Accelerated Thrombolysis of PulMonAry Embolism (ULTIMA) trial was one of the first randomized controlled trials comparing EKOS-assisted CDT to anticoagulation alone. This trial included 59 patients with intermediate risk PEs and concluded that EKOS was superior to anticoagulation alone in reversing right ventricular (RV) dilation at 24 hours.¹⁰⁷ Results from this trial led to the FDA approval of EKOS for the treatment of PE in 2014. In 2015, the results of a single-arm multicenter prospective clinical trial (SEATTLE II) concerning the safety and efficacy of EKOS-assisted CDT in the treatment of acute massive and submassive PEs were published. The investigators concluded that EKOS decreased RV dilation, reduced pulmonary hypertension, decreased thrombus burden, and minimized intracranial hemorrhage.¹⁰⁸ A systematic review and proportional meta-analysis done by Mostafa et al. evaluated the use of EKOS in patients with acute PE. The main finding was that major bleeding rates were 2.3% with EKOS-assisted CDT, in contrast to 10% seen in IVT. They

TABLE 43.4**Dosing of Currently Available Thrombolytic Agents for Pulmonary Embolism**

Agent	Dose
Alteplase	100 mg over 2-h period
Reteplase ^a	10 U + 10 U double-bolus injection, each 10 U over 2-min period, 30 min apart

^aThese dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈ 70 kg) and intravenous injection.

also concluded that EKOS improved postprocedural right to left ventricular diameter ratio, as compared with preprocedural values.¹⁰⁹ The PERFECT trial, published in 2015, also supported the above findings for CDT when used for treatment of massive and submassive PE showing an improvement in mean pulmonary artery pressures from 51.17 ± 14 mm Hg to 37.23 ± 15.8 mm Hg ($P < 0.0001$). There were no major bleeding or procedure-related complications, or hemorrhagic strokes.¹¹⁰ More recently the OPTALYSE PE randomized trial, sponsored by the EKOS Corporation, now owned by United Kingdom-based company BTG, demonstrated that lower doses (4–12 mg) and a shorter infusion time (2–6 hours) had improvement in right to left ventricular diameter ratio and a reduction in clot burden in submassive PE.¹¹¹

Various randomized clinical trials are recruiting patients to further evaluate ultrasound-assisted CDT. Two studies aim to compare standard CDT to ultrasound-assisted CDT and another phase III trial will evaluate the utility of low dose, ultrasound-assisted thrombolysis versus heparin infusion (STRATIFY trial).^{112–114} Additionally, a phase IV trial is enrolling patients to assess low dose IVT vs. CDT with EKOS to treat submassive PE.¹¹⁵

Acute Ischemic Stroke

Well-controlled randomized clinical trials have established the benefits of IVT in patients with AIS^{116–120} (see Ch. 95, Management of Acute Stroke). The 2012 ACCP guidelines recommend administration in less than 3 hours (grade 1A), but extend the window to 4.5 hours (grade 2C) based on data demonstrating continued benefit.²⁵ Of note, the only FDA-approved agent for AIS is rt-PA, although a number of thrombolytic agents, either no longer commercially available or discontinued, have been used in case reports and even clinical trials.^{121–124} Results of one phase II clinical trial comparing alteplase to tenecteplase for the treatment of ischemic stroke suggest neurologic and radiologic outcomes do not differ.¹²⁵ Additionally, a more recent phase II trial (EXTEND-IA TNK) evaluating tenecteplase (dose of 0.25 mg/kg, maximum dose 25 mg) compared to alteplase (0.9 mg/kg, maximum dose 90 mg) within 4.5 hours of symptom onset and prior to thrombectomy found that tenecteplase had a higher rate of reperfusion (22% vs. 10%, $P=0.002$) and improved 90-day functional outcomes.¹²⁶ These outcomes lead to the 2019 American Heart Association/American Stroke Association (AHA/ASA) to

update their guidelines stating that tenecteplase is a reasonable choice over alteplase in patients who are eligible to undergo mechanical thrombectomy, although a weak recommendation (IIb).¹²⁷ To evaluate alteplase dosing, a randomized controlled trial compared low-dose (0.6 mg per kg of body weight) versus standard-dose (0.9 mg per kg of body weight) intravenous alteplase in AIS. The study showed low-dose alteplase to be non-inferior to standard-dose alteplase for the treatment of acute stroke. Low-dose alteplase had a lower incidence of symptomatic intracranial hemorrhage, and lower incidence of early fatal events.¹¹⁶ However, guidelines continue to recommend the standard 0.9 mg/kg dose (not to exceed 90 mg), with a 10% loading bolus, for treatment of AIS¹²⁷ (Table 43.5).

IVT with rt-PA administered within 3 hours of AIS in combination with CDT, or CDT with EKOS for distal thrombus, was studied in 81 patients in a phase II trial Interventional Management of Stroke (IMS)-II.¹¹⁷ Compared with historic data from the National Institute of Neurological Disorders and Stroke, the 3-month mortality was lower (16%), but symptomatic ICH was higher (9.9%).¹¹⁷ In the phase 3 trial (IMS-III), patients who received IVT with rt-PA within 3 hours after stroke symptom onset were randomly assigned to receive either additional IVT or CDT with rt-PA.¹²⁸ After randomizing 665 patients, the study was terminated because no difference was demonstrated in stroke outcome between the two therapies. A concurrent study from the SYNTHESIS Expansion Investigators also demonstrated no benefit to CDT with rt-PA when compared to IVT alone.^{117,118} This is consistent with an earlier phase I study, the Emergency Management of Stroke (EMS) trial, which studied CDT alone against CDT with IVT in 35 patients and found no difference in clinical outcomes or rates of symptomatic ICH.¹¹⁹ However, a prospective observational study of 2650 patients with ischemic stroke showed that percutaneous mechanical thrombectomy in conjunction with CDT or IVT showed improved functional outcome (common odds ratio, 1.84; 95% confidence interval, 1.32 to 2.57) and decreased mortality (15% vs. 33%, $P < 0.0001$) when compared to IVT alone.¹²⁰ Furthermore, in a meta-analysis of five randomized controlled trials, mechanical thrombectomy demonstrated better functional outcomes compared to medical management with IV t-PA alone.¹²⁹

The 2012 ACCP guidelines recommend intra-arterial rt-PA in patients with AIS due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV rt-PA (past the 3- to 4.5-hour window) but are still within 6 hours of symptom onset. They recommended against combined IVT and intra-arterial rt-PA or mechanical thrombectomy, except in carefully selected patients willing to accept an increased risk with uncertain benefit. It should be noted that these recommendations were all grade 2C, weak with low quality of evidence.¹³⁰ More recent 2019 guidelines from the AHA/ASA give a strong recommendation (IA) that IV alteplase should be administered to those meeting criteria even if those patients are also being considered for mechanical thrombectomy. Additionally, due to the reported benefits of mechanical thrombectomy in multiple randomized controlled trials, they recommend its use when patients meet the following criteria: had a normal modified Rankin score prior to stroke, the anterior circulation

TABLE 43.5**Dosing of Currently Available Thrombolytic Agents for Acute Ischemic Stroke**

Agent	Dose
Alteplase	Systemic: 0.9 mg/kg total dose (not to exceed 90 mg): Load 10% as a bolus over 1-min period and infuse remainder over 60-min period Catheter directed: 2 mg bolus (over 2 min) distal to thrombus, then 2 mg bolus (over 2 min) into the thrombus; then infusion 9 mg/h for up to 2 h – not to exceed 120 min (based on the IMS study) ¹²⁴

Dosages are for adult use (≈ 70 kg).

is affected, are older than 18 years, meet appropriate defined stroke scores, and therapy can be initiated within 6 hours, class I (strong) and level A evidence.¹²⁷

Acute Limb Ischemia

Initial evidence that thrombolysis could effectively treat acute arterial occlusions of the extremity and delay or replace surgical interventions came from several nonrandomized case series.^{131,132} Preliminary studies proved CDT to be safer and more efficacious than IVT for all the reasons discussed previously.^{21,22} Three randomized, prospective clinical trials provided definitive evidence that in patients with acute limb ischemia of less than 14 days of duration, CDT was of clinical benefit (see Ch. 104, Acute Limb Ischemia: Surgical and Endovascular Treatment).

The Rochester Trial randomized 114 patients with less than 7 days of limb-threatening ischemia to either open surgery or CDT with UK. The 12-month limb salvage rates (82%) were similar, but thrombolysis provided improved 12-month survival (84% with CDT vs. 58% with surgery, $P = 0.01$).³⁹

The Surgery Versus Thrombolysis for the Ischemic Lower Extremity (STILE) trial included patients with up to 6 months of ischemic symptoms. It compared open surgical therapy with CDT using either rt-PA or UK. The study was stopped after 393 patients, due to adverse primary outcomes in the CDT group when compared with the surgical group. However, a subgroup analysis of patients with less than 14 days of ischemia showed a lower amputation rate at 6 months when treated with CDT than when treated surgically (CDT 11% vs. surgery 30%, $P = 0.02$).⁴⁰

The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial randomized 544 patients with acute (<14 days) arterial or bypass graft occlusion to open surgery versus CDT with UK. At 12 months, rates were similar for amputation-free survival (CDT 65% vs. surgery 75%) and mortality (CDT 20% vs. surgery 17%). While CDT allowed 40% of patients to avoid a surgical intervention, this cohort experienced an increased rate of major bleeding (CDT 12.5% vs. surgery 5.5%, $P = 0.005$).³⁸

Current recommendations support CDT in patients with Rutherford class I and class IIa limb ischemia of less than 14 days duration.^{23,24} In select circumstances, treatment may also be of value in patients with Rutherford class IIb. The enthusiasm for this recommendation is tempered by the time required for successful CDT and the associated bleeding complications

with currently available thrombolytic agents.^{23,24} Contemporary dosing for CDT has evolved to a low-dose extended infusion (Table 43.6). A Cochrane review in 2009 found that although high-dose and forced-infusion techniques achieved vessel patency in less time than low-dose infusion, bleeding complications were more common and at 30 days there was no improvement in patency rates or limb salvage.¹³³ Similarly, a 2019 systematic review of 106 studies, including 19 RCTs, found that CDT-related bleeding complications are not rare (18% of patients) and that lower-dose CDT infusions had similar patency rates to higher-dose treatments, but with decreased bleeding complications.¹³⁴

CDT with EKOS may allow for even lower dosing of thrombolytic agents with equal efficacy and improved safety. A Dutch randomized trial (DUET) comparing CDT with EKOS-assisted CDT for thromboembolic infrainguinal disease showed significantly reduced thrombolysis time for EKOS-assisted CDT (17.7 ± 2.0 hours) compared with CDT alone (29.5 ± 3.2 hours, $P = 0.009$).¹³⁵ Subsequent studies demonstrate real-world effectiveness of EKOS, with high limb salvage results.^{136,137}

A retrospective review analyzed 154 patients with acute limb ischemia who were treated with CDT or pharmacomechanical thrombolysis (PMT), with other adjunctive endovascular and surgical interventions. Technical success was achieved in 84% with a 30-day mortality rate of 5.2% and an overall rate of major amputation of 15%. CDT and PMT had equal benefit. Additional revascularization procedures, mostly endovascular (69%), were required in 89% of patients. End stage renal failure and poor pedal outflow were predictors of limb loss, whereas method of thrombolysis treatment was not. However, PMT was a predictor of technical success compared to CDT.¹³⁸ Moreover, early experimental studies looking at contrast-enhanced ultrasound to accelerate the thrombolytic effects of low-dose CDT in arterial occlusions have shown results in porcine models sufficient to warrant clinical studies.¹³⁹ Alternative methods for thrombus removal also include aspiration mechanical thrombectomy with early promising results, however clinical trials are necessary to compare its effectiveness relative to CDT.¹⁴⁰ Currently a prospective registry is collecting outcomes of aspiration mechanical thrombectomy.¹⁴¹

Deep Venous Thrombosis

Initially, most data on thrombolysis in the management of DVT had been predicated on small randomized clinical trials or venous registries. In 1984, Goldhaber pooled data from six small, randomized studies ($N = 185$) of IVT with SK versus heparin for the management of DVT. Venous patency was achieved 3.7 times more often in patients treated with SK compared to heparin, but bleeding was 2.9 times greater with SK.

A 2005 review by Janssen et al. identified 18 randomized controlled trials of IVT for DVT. Twelve studies compared SK with heparin in 468 patients, two trials compared UK with heparin in 117 patients, and four trials compared rt-PA with heparin in 150 patients. Only one trial compared CDT with standard anticoagulation, and no trials compared PMT with conventional anticoagulation.¹⁴² The conclusion, similar to that of Goldhaber, was that IVT can improve venous patency

TABLE 43.6

Dosing of Currently Available Thrombolytic Agents for Acute Limb Ischemia

Agent	Dose
Alteplase	Catheter directed: Low-dose (extended infusions >12 h): 0.5–2.5 mg/h High-dose: 0.05 mg/kg per hour up to 12 h (or until maximum of 100 mg administered)
Reteplase ^a	Catheter directed: 2-U bolus, then infuse 0.5–1U/h (should not exceed a total administered dose of 20 U)
Tenecteplase ^a	Catheter directed: 0.25–0.5 mg/h; infusion stopped if no improvements on serial arteriograms

^aThese dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈ 70 kg).

but with an increased risk of bleeding. A subsequent Cochrane review of 17 randomized controlled trials involving 1103 patients demonstrated that when compared to anticoagulation alone, IVT was associated with lower risk of post-thrombotic syndrome (PTS), and leg ulceration; but with a higher bleeding risk (RR: 2.23; 95% CI: 1.4 to 3.5, $P = 0.0006$).¹⁴³ To examine whether CDT could decrease the bleeding risk, Mewissen et al. established a venous registry that included 63 institutions and 287 patients. A higher frequency of venous patency was reported for CDT than for anticoagulation, but major bleeding complications still occurred in 11% of the patients.¹⁴⁴

Before 2012, only one randomized trial had compared CDT with anticoagulation. In 2002, Elsharawy et al. randomized 35 patients with acute iliofemoral DVT and found that those treated with CDT as opposed to anticoagulation had an improved 6-month patency (72% vs. 12%, $P = 0.0001$) and less venous reflux (11% vs. 41%, $P = 0.04$).¹⁴⁵ In 2012, the Catheter-Directed Thrombolysis Versus Standard Treatment for Acute (<21 days) Ilio-femoral Deep Vein Thrombosis (the CaVenT study) trial randomized 209 patients to CDT versus anticoagulation alone. After 6 months, iliofemoral vein patency was higher in the CDT group (66%) versus the anticoagulation group (47%, $P = 0.012$), and at 24 months, rates of PTS were lower in the CDT group (41.1%) compared with the anticoagulation group (55.6%, $P = 0.047$). However, 20 bleeding complications related to CDT occurred, including three major bleeding complications.¹⁴⁶

Engelberger performed a prospective single center study in 87 patients with iliofemoral DVT using EKOS-assisted CDT. Primary and secondary patency rates at 1 year were 87% and 96%, respectively. PTS at 1 year was 6%, and the incidence of major bleeding was 1%.¹⁴⁷ In a later open-label randomized controlled study of 48 patients, they compared EKOS-assisted CDT with CDT alone and found that there was no difference in long-term outcomes.¹⁴⁸

Debate continues on whether the DVT clearance and immediate patency achieved by thrombolysis translates into superior long-term outcomes. The current guidelines favor anticoagulation over CDT (grade 2C) for an acute proximal and

leg DVT. The ACCP stipulates that CDT (with or without PMT) or IVT can be considered if patients attach a high value to the prevention of PTS and a lower value to the initial complexity, cost, and risk of bleeding. Additionally, they state that those most likely to benefit from CDT are patients with symptoms for less than 14 days, iliofemoral DVT, good functional status, a low risk of bleeding, and a life expectancy of greater than one year.²⁵ Current recommended CDT dosing to treat DVT is described in Table 43.7 (see Ch. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment).

More recently, the Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis (ATTRACT) trial, a randomized controlled, open-label, blinded phase III trial, was conducted to compare anticoagulation alone to anticoagulation with PMT. While no significant difference was found in PTS risk between the groups, they identified a significant reduction in moderate to severe PTS in those receiving PMT (24% vs. 18%, $P = 0.04$) and a decrease in severity scoring and leg pain. However, the PMT group demonstrated a higher risk of major bleeding.¹⁴⁹ Another randomized controlled phase III trial, DUTCH CAVA, evaluated outcomes of EKOS CDT versus anticoagulation alone. They randomized 184 patients and found that EKOS CDT did not affect the risk of PTS at 1 year (EKOS 29% vs. anticoagulation 35%, $P = 0.42$), and had a higher rate of major bleeding (EKOS 5% vs. anticoagulation 0%).¹⁵⁰

Arteriovenous Access Occlusion

The use of thrombolysis in patients with AVG thrombosis was reported as early as 1983, when Rodkin et al. used SK to successfully lyse eight of nine thrombosed AVGs.¹⁵¹ Over the years, a number of techniques have been developed that have made thrombolysis quite efficient and clinically effective to treat both AV fistula and graft thrombosis. The cross-catheter method uses two overlapping catheters placed at separate locations within the access, with their tips just past the arterial inlet and venous outlet.^{26,152} The “lyse and wait” technique is a method in which the thrombolytic agent is infused into the graft while the arterial and venous ends are manually occluded. With the advent of PMT devices, thrombolytic agents are being used as an adjunct following thrombus extraction.^{153–155} Although no FDA-approved thrombolytic agents are available for the treatment of AVG occlusion, case reports and retrospective series exist for almost every agent.^{156–160} A recent study of 294 patients (156 AV fistulas and 138 AV grafts) demonstrated high technical and clinical success rates using UK and alteplase for thrombolysis, with better patency rates in the fistula group. They found that recurrent thrombosis within 90 days was negatively associated with short- and long-term patency.¹⁶¹ Ultrasound-guided PMT has also been described for AV access thrombosis with successful patency rates, recognizing that rethrombosis rates can be high, although most can be retreated with PMT.¹⁶² Thrombolytic doses of 2 mg of rt-PA, 1 mg of tenecteplase, and 1 unit of reteplase have all been used with success and minimal to no

TABLE 43.7

Dosing of Currently Available Thrombolytic Agents for Venous Thrombosis

Agent	Dose
Alteplase ^a	Catheter directed: 0.25–2 mg/h
Reteplase ^{a,b}	Catheter directed: 0.75 U/h
Tenecteplase ^{a,b}	Catheter directed: 0.25–0.5 mg/h

^aInfusions are stopped once no improvement is seen on serial venograms performed every 8 to 12 hours.

^bThese dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈ 70 kg).

TABLE 43.8

Dosing of Currently Available Thrombolytic Agents for Arteriovenous Graft Occlusion

Agent	Dose
Alteplase ^{a,b}	Catheter directed: 2 mg
Reteplase ^{a,b}	Catheter directed: 1 U
Tenecteplase ^{a,b}	Catheter directed: 1 mg

^aThese dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.

^bThe listed dosages are administered under fluoroscopic guidance. Dosing can be repeated if arteriovenous graft patency is not restored. Dosages are for adult use (≈ 70 kg).

bleeding complications (Table 43.8) (see Ch. 177, Hemodialysis Access: Failing and Thrombosed).

Central Catheter Occlusion

The only FDA-approved thrombolytic for central catheter occlusion is rt-PA marketed in 2-mg vials as Cathflo. Its efficacy was studied in 1064 patients in the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) trial. Increased catheter patency was seen after 2 hours with one 2 mg dose of rt-PA (74%) compared to placebo (17%, $P = 0.0001$).¹⁶³ Efficacy rates were similar among catheter types (single-, double-, and triple-lumen catheters and ports), and 30-day adverse events were rare: ICH (0.0%), embolic events (0.0%), gastrointestinal bleeding (0.3%), thrombosis (0.3%), and sepsis (0.4%).¹⁶⁴ An additional benefit of thrombolytic use to restore central venous catheter patency rather than replacement is decreased cost, however length of stay and readmission rates do not differ.¹⁶⁵ Interestingly, while alteplase is safe and effective, newer thrombolytic agents may have similar profiles but require shorter treatment times¹⁶⁶ (Table 43.9).

In children, rt-PA has also been found to be safe and effective through the Cathflo Activase Pediatric Study (CAPS). Patients weighing less than 30 kg received instillations of rt-PA (1 mg/1 mL) equal to 110% of the estimated internal lumen volume of the dysfunctional central venous catheter, not to

TABLE 43.9**Dosing of Currently Available Thrombolytic Agents for Catheter Occlusion**

Agent	Dose
Alteplase ^a	≥30 kg: 2 mg in 2 mL; may repeat after 120 min if catheter still occluded ≤30 kg: 110% of the internal lumen volume (not to exceed 2 mg in 2 mL); may repeat above after 120 min if catheter still occluded
Reteplase ^{a,b}	0.4 U in 2 mL; may repeat after 30–60 min if catheter still occluded
Tenecteplase ^c	2 mg in 2 mL into each lumen for 1 hour dwell time; drug withdrawn after dwell time

^aThe volume instilled is not to exceed the internal lumen volume. Clamp the catheter and try to aspirate its contents in 30 minutes. If no result, a second dose can be attempted (see individual agents for timing).

^bThese dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.

^cDosing guidelines are based on clinical trials evaluating this medication use specifically for hemodialysis catheters. Efficacy and safety when used with other central venous catheters is not described and no clinical trial exists.

Dosages are for adult use (≈ 70 kg).

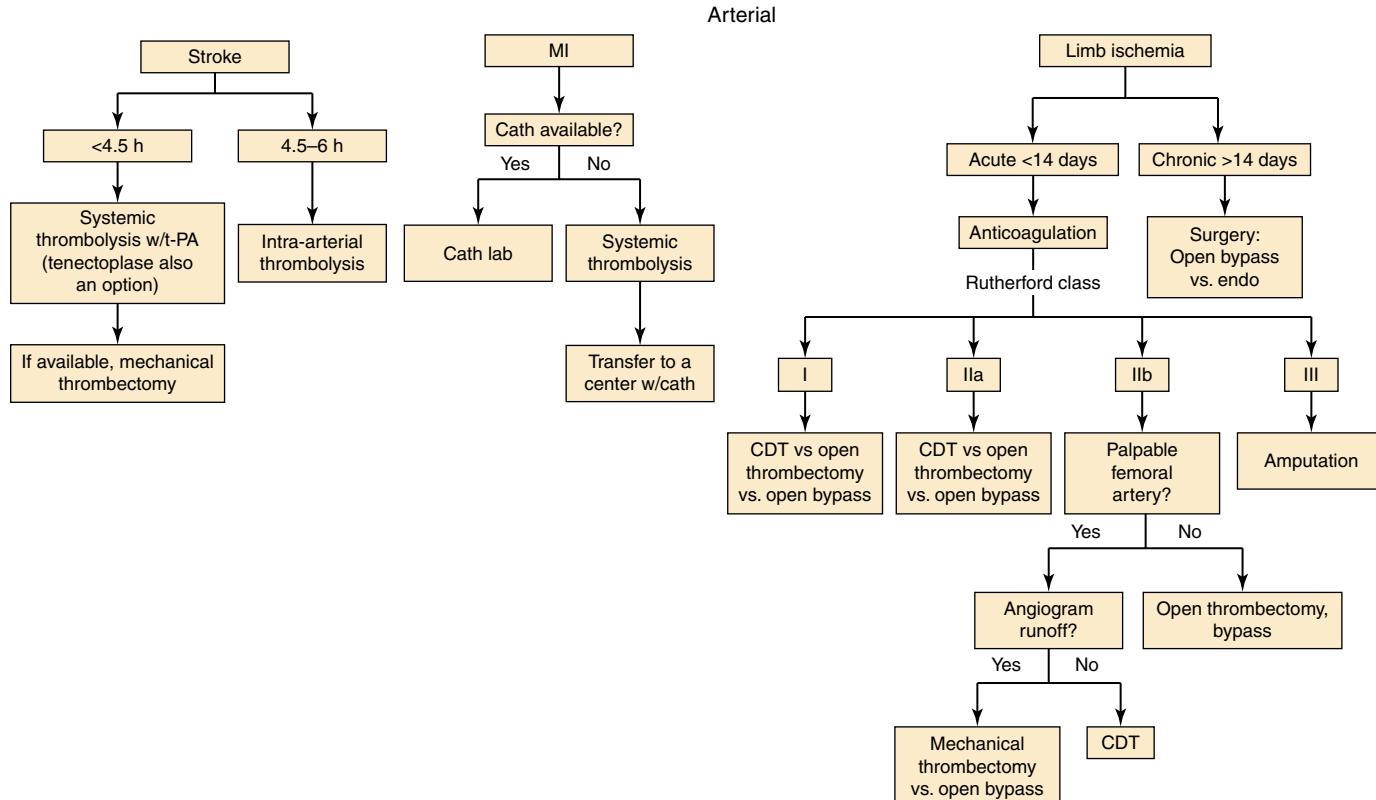
exceed 2 mL.¹⁶⁷ A recent meta-analysis also demonstrated the safety and efficacy of thrombolysis of central catheters in the pediatric population across multiple studies.¹⁶⁸

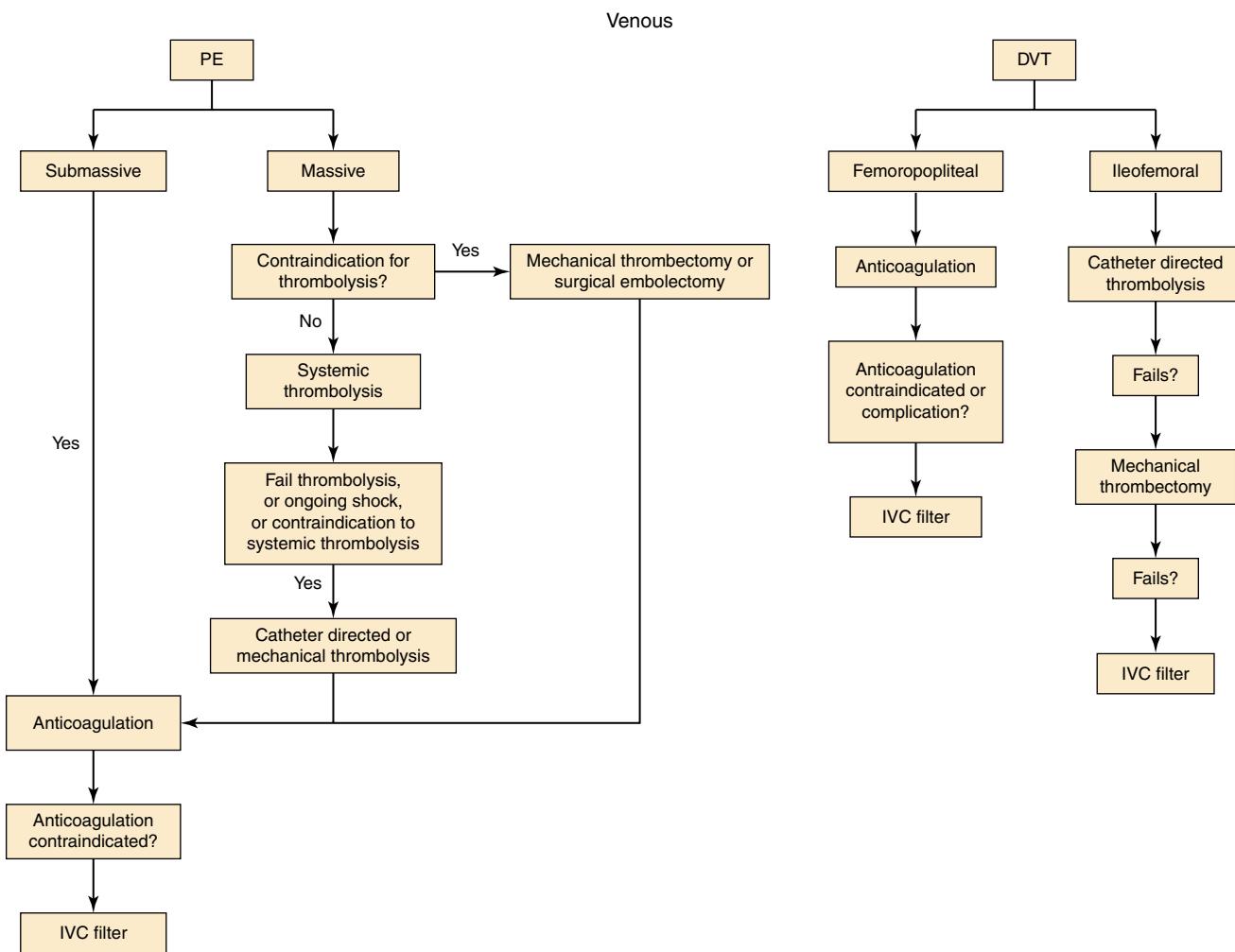
Hemodialysis catheters were excluded from all clinical trials on Cathflo; therefore, hemodialysis catheters are not included

in the FDA indication for catheter occlusion. However, the successful use of rt-PA (2 mg), reteplase (0.4 U), and tenecteplase (2 mg in each lumen) has been reported.^{169–172} Randomized, international, placebo-controlled and open-label studies (TROPICS 3 and 4) have evaluated the use of tenecteplase and demonstrated improved blood flow rate when used for dysfunctional hemodialysis catheters.^{173–175}

Miscellaneous Uses

Intraoperative thrombolytic therapy used as an adjunct to open arterial thrombectomy or thromboembolectomy has been described and shown to be safe and effective in breaking down distal thrombus.¹⁷⁶ However, in patients with extensive distal clot burden, thrombolytic boluses given intraoperatively may not be enough. In these circumstances, isolated limb perfusion with high-dose thrombolysis has been described with or without a pump oxygenator. Another purported advantage of this treatment is the mitigation of the systemic effects of reperfusion injury.¹⁷⁷ Although combining open surgical procedures with thrombolysis is infrequently employed, there may be selected patients in which knowledge of these techniques can be limb and/or life sparing. A recent study of patients who presented with moderate acute limb ischemia due to popliteal artery aneurysm thrombosis found that major adverse limb events were lower and overall survival was higher in patients who underwent intraoperative thrombolysis.¹⁷⁸ Still, larger and randomized clinical trials are warranted to evaluate the efficacy and clinical utility of this therapeutic method.

CHAPTER ALGORITHM



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Systemic Complications: Cardiac

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INTRODUCTION	564	Positron Emission Tomography	569
PATHOPHYSIOLOGY OF MAJOR ADVERSE CARDIAC EVENTS	565	Computed Tomography Coronary Angiography	569
Myocardial Infarction	565	PREOPERATIVE CORONARY ANGIOGRAPHY AND REVASCULARIZATION	569
Congestive Heart Failure	566	BEST MEDICAL THERAPY TO REDUCE PERIOPERATIVE CARDIAC COMPLICATIONS	570
Arrhythmias	566	Beta Blockade	570
DEFINITION AND OPTIMIZATION OF CARDIAC RISK PRIOR TO SURGERY	567	Statins	570
Cardiac Risk Indices	567	Aspirin	570
Preoperative Blood Work and Risk of MACE	567	Dual Antiplatelet Therapy After Coronary Stenting	570
<i>Natriuretic Peptides, Tropoenin and Inflammatory Markers in Predicting MACE</i>	567	INTRAOPERATIVE VARIABLES IMPACTING MACE	571
Resting Electrocardiogram	568	Type of Anesthetic Technique and Agent Utilized	571
Noninvasive Imaging	568	Intraoperative Blood Loss and Transfusion	571
PREOPERATIVE EVALUATION FOR CORONARY ARTERY DISEASE	568	Intraoperative Blood Pressure Management	572
Single Photon Emission Tomography	568	Hypothermia	572
Cardiac Magnetic Resonance Imaging		POSTOPERATIVE MANAGEMENT OF CARDIAC COMPLICATIONS	573
Stress	569	CHAPTER ALGORITHMS	574
Dobutamine or Exercise Stress Echo	569		

INTRODUCTION

The maxim that “it is not the kind of disease the patient has rather the kind of patient that has the disease” is apropos since symptomatic vascular disease frequently occurs in the kind of patient that also has multiple cardiac risk factors.^{1,2} The underlying cardiac conditions common to this patient population, coupled with the frequent perioperative hemodynamic changes and perturbations of the clotting cascade, create the perfect milieu for a major adverse cardiac event (MACE). The most common perioperative MACE is myocardial infarction (MI), followed by atrial fibrillation, acute heart failure, or a

combination thereof with individual patient risk varying based on the type, indication, and urgency of vascular surgery.³ Cardiac death is generally related to a cascade of events following myocardial injury culminating in cardiogenic shock or recalcitrant arrhythmias.⁴ In the highest risk vascular surgical categories of lower extremity bypass, aorto-femoral bypass and abdominal aortic aneurysm repair, the expected MACE and mortality is 9.8%–21.7% and 2.0%–3.3%, respectively.^{3,5,6} Accordingly, the vascular surgical team must be armed with foundational knowledge regarding clinical manifestation, pathophysiology and risk mitigation of cardiac complications during or following surgery.

PATHOPHYSIOLOGY OF MAJOR ADVERSE CARDIAC EVENTS

Myocardial Infarction

One of the most feared complications during, or following, vascular surgery is MI, which occurs in 1.6% to 17% of patients depending on how MI is defined.^{4,7} In 2007 a global task force set out to develop a pathophysiology-based universal definition for MI to align nomenclature used by clinicians and researchers around the world.⁸ The Universal Definitions of MI have evolved through the years with the 2018 4th edition dividing the cause of acute cardiac troponin (cTn) leak into two entities: ischemic (“MI”) and nonischemic (“myocardial injury”).^{9,10} The MI category is further divided into five different types. Type IV and V are cTn-positive events following coronary interventional and heart surgical procedures, respectively, and thus not pertinent to this discussion. A “type III MI” occurs when there are typical symptoms or EKG changes suggesting MI followed by cardiac arrest and death before enzymes can be obtained. This diagnosis may be considered in some of our vascular surgery cases depending on the clinical manifestations leading up to a cardiac arrest or sudden death while the patient is still hospitalized. It should be noted that if patients are diagnosed with a type III MI and subsequently found to have vessel thrombosis on autopsy, the diagnosis is then changed to type I MI.⁹ The most common Universal Definition cTn positive events following vascular surgery are the MI (type I or II) and “cardiac injury” with associated pathophysiology detailed below.

The type I MI occurs when plaque rupture is triggered by perioperative vessel-wall shear stress, hemodynamic changes, activation of the inflammatory cascade (e.g. interleukin 1 and 6, tumor necrosis factor and C-reactive protein) and perturbation of the clotting cascade.^{11–14} These patients have an associated cTn rise and fall and at least one of the following: symptoms consistent with acute myocardial infarction, new ischemic changes on the EKG, imaging showing new segmental wall motion abnormality or identification of coronary thrombosis on catheterization or autopsy.⁹

The type II MI has very similar requirements as type I but has the absence of coronary thrombosis.⁹ Due to the similarities it may be difficult to differentiate a type I and II MI without left heart catheterization or autopsy. In general, patients who have not undergone left heart catheterization and do not have postoperative ST elevation or new LBBB on EKG most often have a type II MI, which is the dominant cause of cardiac enzyme leak after vascular surgery.¹⁵ The diagnosis of type II MI has likely increased as the fidelity (sensitivity and specificity) of cardiac enzymes have improved dramatically.¹⁶ Keep in mind, a type II MI can be caused by increased oxygen demand in the presence of fixed coronary artery occlusive (inadequate flow reserve) in the absence of plaque instability or thrombus. This becomes very important as patients improperly labeled with type I MI are often adjudicated by outside quality peer review analysis in a way that can adversely impact hospital MI outcomes data.^{15,17} Type II MI patients may lack associated

significant coronary artery disease but have microvascular disease or other concomitant structural issues within the myocardium that limit tolerance to extreme changes in oxygen demand during major vascular surgery.¹⁸

To further complicate matters, some patients will have the typical rise and fall of cTn but lack the EKG changes, segmental wall motion changes or other findings to support the diagnosis of a type I or type II MI during or following surgery. In this case, the event is defined as “myocardial injury” due to cardiomyocyte death or injury unrelated to ischemia.⁹ We see these types of events when the right or left ventricle is placed under strain that exceeds the boundary conditions predicted by the Frank–Starling curve, resulting in nonischemic stretch injury to cardiac myocytes. It can also be caused by severe metabolic derangements, catecholamine excess and cardioversion.

Many of our surgical and perioperative medicine colleagues have suggested describing the perioperative cardiac enzyme leak (irrespective of MI type) as “myocardial injury after noncardiac surgery” (MINS) or perioperative myocardial injury after surgery (PMI).^{19,20} We believe this adds confusion to the literature since “myocardial injury” is defined differently in the most recent multidiscipline global Universal Definitions described above.⁹ However, elevated high-sensitivity cTn is seen in 1 in 7 of patients after noncardiac surgery with an associated 9% and 22% 30-day and 1-year mortality, respectively.²⁰ There is also a linear relationship between increasing levels of cTn release and 30-day mortality ranging from 0.5% (cTn <20 ng/L) to 29.6% for cTn of >1000 ng/L.²¹ Positive high-sensitivity cTn is even more common after vascular surgery (1 in 5 patients) and is associated with an eightfold increase in 30-day mortality.^{19,20,22,23} It’s unclear today if cTn leak is a predictor of mortality due to the direct impact of the MI/injury or because the presence of positive cardiac enzymes self-selects patients that would ultimately be at the highest risk of mortality. Irrespective, enzyme leaks are proven to be a marker of increased risk of mortality postoperatively and should not be dismissed as a biological epiphenomena.²⁴ To simplify the different types and causes for cardiac myocyte injury, a modified algorithm for vascular surgery patients is provided with emphasis on the relevant 4th Universal Definition of MI criteria with the inclusion of where MINS fits into this clinical spectrum (see Chapter Algorithm 1).

Unfortunately, some patients with poor cardiac reserve or a large burden of perioperative cardiomyocyte insult may face a continuum of pathophysiologic substrates as detailed in **Figure 44.1**. For example, patients who are experiencing a large type I infarction, or a new type I infarction superimposed on baseline poor LV function, may subsequently develop an oxygen demand mismatch type II MI due to compensatory changes in the non-infarct zone or from associated poor perfusion due to declining cardiac output. Subsequently, these patients develop compensatory dilation of the left ventricle with progressive LV strain and alongside worsening acidemia there can be direct nonischemic myocardial injury as well. These patients digress into the so-called “spiral” to progressive cardiogenic shock and often do not survive.

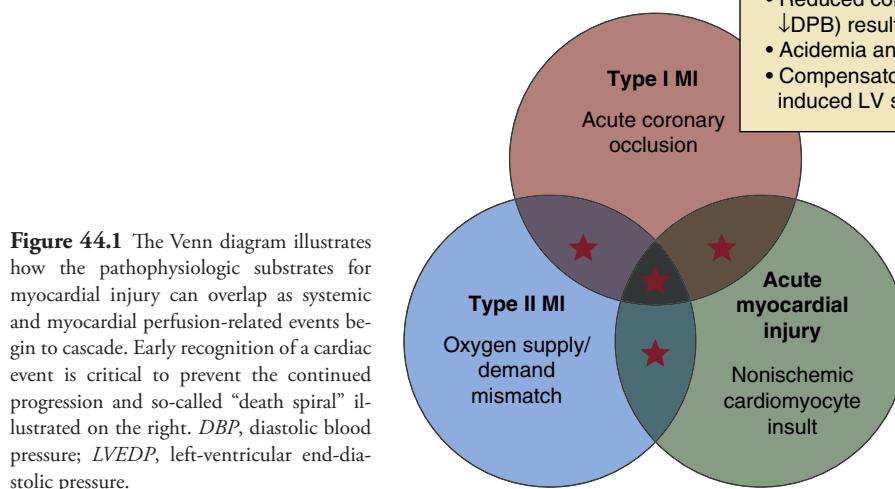


Figure 44.1 The Venn diagram illustrates how the pathophysiologic substrates for myocardial injury can overlap as systemic and myocardial perfusion-related events begin to cascade. Early recognition of a cardiac event is critical to prevent the continued progression and so-called “death spiral” illustrated on the right. *DBP*, diastolic blood pressure; *LVEDP*, left-ventricular end-diastolic pressure.

Congestive Heart Failure

The pathophysiology and etiology of congestive heart failure (CHF) before, during or following vascular surgery varies significantly and often a single cause is difficult to fully characterize. Any baseline valvular or left ventricular (LV) function abnormality makes the patient vulnerable to perioperative volume shifts and myocardial insult. In the preoperative assessment of patients over age 65 undergoing major noncardiac surgery, CHF was present in 18% of patients.²⁵ In a Medicare database registry the presence of perioperative CHF was associated with a 63% increase in operative mortality and was a better predictor of re-admission than known coronary artery disease (CAD), although the cause of CHF was not fully elucidated.²⁶ In other studies, patients who have heart failure with preserved ejection fraction (HFpEF) seem to do better perioperatively whereas the degree of reduced LV function in heart failure with reduced ejection fraction (HFrEF) seems to correlate with worse outcomes.^{27–29} Not surprisingly, in patients undergoing vascular surgery the impact of a preoperative diagnosis of CHF dramatically impacts outcome. For example, patients with CHF compared to patients without CHF undergoing infringuinal bypass have a >twofold increase in 30-day mortality and prolonged length of stay (>9 days).³⁰

Preoperative transthoracic echocardiography (TTE) and natriuretic peptides (NTproBNP or BNP) should be obtained in all patients with known or suspected LV dysfunction.²⁵ “Brain” natriuretic peptide (BNP) is a misnomer since it was initially discovered in the ventricles of the porcine brain before subsequently noted to be more abundant in LV myocytes.³¹ BNP release is directly proportional to LV volume expansion as is the inactive prohormone NT-proBNP. The latter has a slightly longer half-life than BNP but more studies in different patient phenotypes are needed before one of these assays could be suggested over the other.³² The natriuretic peptides are strong predictors of postoperative MACE and mortality in vascular surgery patients. While the Canadian perioperative

Spiral of worsening myocardial function

- Decreased coronary perfusion pressure
- Reduced coronary diastolic perfusion gradient (\uparrow LVEDP and \downarrow DBP) resulting in subendocardial type II MI progression
- Acidemia and metabolic disturbances direct myocardial injury
- Compensatory fluid resuscitation and compensatory LV dilation induced LV strain causing direct myocardial cell injury



guidelines suggest obtaining these studies in all major risk surgery patients with or without history of CHF, many centers still reserve these assays for patients with known or suspected LV dysfunction.^{25,33–36}

Another potential etiology and risk factor for CHF is valvular disease and this is particularly true of aortic stenosis (AS) since 2% to 3% of patients over 65 years old have calcific aortic valvular stenosis.³⁷ Unfortunately, many vascular patients with hemodynamic significant aortic stenosis may be asymptomatic due to vascular disease-associated limited activity. It is impractical to screen all patients for AS prior to surgery and the hemodynamic severity of AS cannot be predicted by intensity or harshness of a systolic ejection murmur on exam. The surgeon should be alerted to the presence of significant aortic valve disease if there is delayed carotid or brachial artery upstroke (parvis et tardus) in the presence of a systolic ejection murmur. This finding also can be seen as delayed pulse wave inflection on a radial artery tracing placed at the time of surgery. Severe AS (valve area $\leq 1 \text{ cm}^2$) is associated with increased MACE following major noncardiac surgery.³⁸ While the AS-associated perioperative mortality has decreased it remains high in patients undergoing emergency surgery and is worse in those with concomitant atrial fibrillation or azotemia.³⁸ Symptomatic regurgitant lesions are generally better tolerated but need to be clinically optimized prior to elective vascular surgery.³⁹

Arrhythmias

The most common perioperative arrhythmia is new-onset atrial fibrillation (AFib) and is seen in 4.7% of patients undergoing vascular surgery.⁴⁰ Most often postoperative AFib will spontaneously return to normal sinus rhythm; however, incidental AFib after vascular surgery is associated with significant increases in 30-day MACE, stroke and mortality that is likely explained by the underlying risk factors for this arrhythmia.^{40,41} Atrial fibrillation generally occurs in patients

with baseline abnormalities in left atrial architecture (e.g. fibrosis, cellular ultrastructural defects, and contractile protein abnormalities) with associated electrical and autonomic remodeling.⁴² Often the atrial pathology predisposing to AFib is driven by long-term injury due to valvular or ventricular dysfunction with pressure overload-associated atrial remodeling.⁴² The most common substrate is long-standing hypertension with associated left ventricular diastolic dysfunction.⁴² In these patients, atrial fibrillation alone could precipitate perioperative CHF since the loss of atrial contribution to overall cardiac output is much greater in patients with impaired left ventricular relaxation.

Perioperative ventricular arrhythmias are often associated with ischemia, myocardial injury, electrolyte imbalance or catecholamine excess. Non-sustained ventricular tachycardia (VT) can be seen in as many as 1 in 6 vascular surgery patients but sustained VT and ventricular fibrillation (VF) are seen in only 2% and 1% of patients, respectively.⁴³ Vascular surgery patients with a reduced preoperative ejection fraction have a higher risk of ventricular arrhythmias (VT and VF) and those patients that have perioperative ventricular arrhythmias have a higher risk of sudden cardiac death during follow-up.⁴⁴

DEFINITION AND OPTIMIZATION OF CARDIAC RISK PRIOR TO SURGERY

The role of preoperative cardiac evaluation is never to “clear” the patient for surgery, but rather aid in defining risk and, when possible, advise on risk mitigation. Ideally, preoperative evaluation of high-risk vascular surgery patients should include a multidiscipline team or “shared care model” to adjudicate risk, inform risk mitigation strategies and participate in shared consent.³⁴ The “vascular team” approach is not new and this type of multidiscipline model has been applied in liver transplant, renal transplant, trauma and more recently structural heart disease.⁴⁵ The importance of developing multidiscipline vascular teams has also been highlighted in white papers and was recently granted a Class I, LOE C guidance for PAD patients in ESC guidelines.^{45,46}

There are presently three perioperative care guidelines for noncardiac surgery originating from the US (ACC/AHA), EU (ESC/ESA) and Canada.^{25,34,47} The US and EU guidelines are very similar regarding need for cardiac workup and focus on clinical outcomes whereas the Canadian guidelines are more conservative on CAD workup and emphasize cost effectiveness.⁴⁸ One additional key difference is that the Canadian guidelines published 3 years after the US and EU guidelines are heavily reliant on biomarkers (e.g. cTn and BNP) for risk assessment before and after surgery. The preoperative workup recommendations to follow will track the US and EU guidelines but the reader should be aware that the field is rapidly evolving and these recommendations are subject to change. With that preface, the need for additional preoperative testing or consultation can be aided by Cardiac Risk Assessment models as follows.

Cardiac Risk Indices

The optimal vascular surgery cardiac risk index remains elusive.^{49–51} The Revised Cardiac Risk Index (RCRI) has gained popularity in noncardiac surgery with an overall accuracy ranging between 0.75 and 0.80.⁵² The RCRI has been widely used and was adopted by the ACC/AHA and ESC/ESA guideline committees for the preoperative stratification of a patient’s perioperative cardiac risk.⁵³ However, when limited strictly to studies of vascular surgical populations, a meta-analysis of 24 studies showed that the RCRI had an aggregate sensitivity and specificity of 0.70 and 0.55, suggesting inadequate reliability.⁵⁴

In 2010, the Vascular Study Group of New England (VSGNE) found in a study of over 10,000 patients that the RCRI predicted risk after carotid endarterectomy (CEA) reasonably well, but substantially underestimated risk for low- and higher-risk patients.⁵⁵ In a multivariate analysis of the VSGNE cohort, the independent predictors of adverse cardiac events included: increasing age, smoking, insulin-dependent diabetes, CAD, CHF, abnormal cardiac stress test, long-term beta-blocker therapy, COPD, and elevated creatinine.⁵⁵ The rates of cardiac complications for patients with zero to three, four, five, and greater than or equal to six VSGNE Cardiac Risk Index (VSG-CRI) risk factors were 3.1%, 5.0%, 6.8%, and 11.6% in the derivation cohort and 3.8%, 5.2%, 8.1%, and 10.1% in the validation cohort, respectively.⁵⁵ The authors concluded that the VSG-CRI risk model more accurately predicted the actual risk of cardiac complications in vascular surgery patients than the RCRI.⁵⁵

More recently, the analysis of 88,879 patients in the vascular quality initiative (VQI) registry led to the development of a risk calculator that allowed independent risk assessment for various subtypes of vascular surgery.⁵⁶ The procedure-specific models generated by the VQI Cardiac Risk Index (VQI-CRI) demonstrated improved prediction compared with the all-procedure model, with CEA, INFRA, EVAR, and Open AAA.⁵⁶ Our team now uses the QxCalculate VQI-CRI app as the preferred risk index assessment model for our vascular surgery patients.⁵⁶ However, we anticipate as biomarker assays improve and artificial intelligence matures we will see a movement towards personalized risk assessment based on patient phenotypes, comorbidities, biomarkers and type/urgency of vascular surgery.

Preoperative Blood Work and Risk of MACE

Selection of screening bloodwork before vascular surgery is highly dependent on clinical variables that may impact overall risk, including but not limited to comorbidities and medications (see Ch. 34, Preoperative Evaluation and Management).

Natriuretic Peptides, Troponin and Inflammatory Markers in Predicting MACE

Increased preoperative levels of plasma NT-proBNP and BNP have been associated with increased postoperative adverse outcomes as detailed above. The risk of cardiovascular death and nonfatal MI has a linear relationship with postoperative BNP (BNP <30 pg/mL 0.11 risk to BNP >116 pg/mL 6.4-fold

risk).⁵⁷ The advent of high sensitivity cTn assays has led to the awareness that patients with baseline cardiovascular anomalies may have elevated high-sensitivity cTn.^{58,59} A single-center observational study found that the 3-month risk of cardiac complications after major elective vascular surgery could better be predicted preoperatively by adding pro-BNP with high sensitivity cTn to preoperative clinical risk scores but this has not yet been validated in US and EU Guidelines.⁶⁰

It was demonstrated that patients undergoing lower extremity bypass with an elevated preoperative high-sensitivity C-reactive protein hsCRP >5 mg/L had a higher incidence of major postoperative vascular events (60%) compared with 32% in those with a baseline hsCRP of <5 mg/L ($P = 0.004$). Following multivariable analysis, elevated hsCRP correlated with adverse graft-related or cardiovascular events.⁶¹ Vascular surgery patients with high pre-intervention values of both hsCRP and NT-BNP were 10.6 times more likely to experience MACE than were patients with normal hsCRP and NT-BNP values.⁶²

While some have advocated the routine use of biomarkers in the pre- and/or postoperative period for all noncardiac surgery, this remains a Class III (LOE C) indication for low-risk patients based on the ESC perioperative guidelines versus being encouraged in the more recent Canadian guidelines.^{25,34} It is reasonable to assess preoperative troponin and/or NT-proBNP or BNP in high-risk or major surgery patients (Class IIb, LOE B) and we presently use these biomarkers in select patients (e.g. complex high risk surgery, known poor LV systolic function, known treated 3-vessel coronary disease and <1 year history of coronary DES).²⁵ The Canadian perioperative guidelines emphasize that measuring NT-proBNP or BNP before noncardiac surgery can enhance perioperative cardiac risk estimation in patients who are 65 years of age or older, are 45–64 years of age with significant cardiovascular disease, or have an RCRI score ≥ 1 (strong recommendation; moderate-quality evidence), but routine use of biomarkers has not yet become standard practice in many other countries.³⁴

Resting Electrocardiogram

Preoperative ECG is recommended for all patients undergoing vascular surgery (Class I, Level C).⁶³ New resting ST-segment ECG changes may require additional workup, depending on the urgency of the planned vascular surgery. However, most preoperative ECG abnormalities represent chronic changes that must be considered in the clinical context of overall risk.⁵² Patients with pathologic Q-waves or LVH are more likely to have perioperative ischemia or infarction.⁶⁴ In one study of patients undergoing noncardiac surgery, preoperative bundle branch blocks, Q waves, and ST-T changes were significant predictors of postoperative cardiac events, however their predictive power was lost with multivariable logistic regression that included the six RCRI independent risk factors.⁶⁵ Accordingly, chronic ECG changes alone should not be used to adjudicate MACE risk.

Noninvasive Imaging

Signs of cardiac failure on chest X-ray should trigger further examination to gain better understanding of the potential

underlying causes of the cardiac dysfunction.^{47,66} Routine pre-operative echocardiography is not recommended for screening in low to intermediate risk patients in the absence of specific indications.^{47,66} However, echocardiography should be considered in patients with known history of CHF or with worrisome chronic Q-waves or poor R-wave progression on ECG.^{47,66} Additionally, echocardiography may be reasonable in high-risk surgery patients without symptoms as a Class IIb, Level C indication to assess LV, RV and valve function.⁶³ In patients undergoing emergent high-risk vascular surgery we often use hand-held point of care ultrasound to quickly scan for occult AS or poor LV function.

PREOPERATIVE EVALUATION FOR CORONARY ARTERY DISEASE

Over 30 years ago we learned 90% of patients undergoing vascular surgery had CAD and as many as 5% had left main disease and 11% severe 3-vessel disease.⁶⁷ We have detailed the pathophysiology of perioperative MI above and recognize postoperative MACE is higher in patients with severe CAD when compared to coronary angiogram adjudicated controls.⁶⁸ Therefore, identifying patients with severe, and often clinically silent, coronary disease has been the focus of many risk-mitigation strategies. The selection of which patients will benefit from exercise stress testing, stress imaging or heart catheterization prior to vascular surgery can be challenging. To simplify this discussion, it is clear that the low-risk surgical procedures in asymptomatic patients or patients with stable symptoms do not require cardiac imaging stress testing (Class III). We have provided a simplified algorithm for suggested cardiac imaging and catheterization strategy based on our interpretation of the current ACC/AHA and EU guidelines (see Chapter Algorithm 2).

In patients who require additional cardiac evaluation, the selection of testing modality is highly dependent on the regional and center expertise since the quality of the imaging equipment and accuracy of image interpretation vary from institution to institution. In general, the imaging modalities are comparable but there are some clinical variables to consider.

Single Photon Emission Tomography

SPECT remains the most commonly used cardiac imaging test for preoperative evaluation in noncardiac surgery and is widely available with reproducible results. The radiation exposure for SPECT with dual isotope is 24 mSv versus a Tc-99 low-dose stress at only 4 mSv (comparison: individuals between 2000 and 3000 yds from ground zero at Hiroshima had a mean dose of 29 mSv and a chest X-ray has 0.1 mSv).⁶⁹ Thus SPECT will add to the cumulative radiation dose if periprocedural angiography or future imaging is needed. Additionally, overweight patients and women are subject to attenuation artifact (false-positive studies). Also, use of pharmacologic agents (e.g., adenosine, dipyridamole and regadenoson) may be associated with bronchospasm, hypotension and AV block.

Cardiac Magnetic Resonance Imaging Stress

CMR has excellent spatial resolution and, in a meta-analysis, CMR was shown to have better sensitivity (89%) and specificity (76%) than SPECT for detecting significant CAD.⁷⁰ CMR provides insight into LV wall thickness and can add additional information in patients with suspected structural heart disease. The study cannot be used in patients with significant chronic kidney disease or in patients with implants that are not MRI compatible. The use of pharmacologic agents (e.g., adenosine, dipyridamole and regadenoson) may be associated with bronchospasm, hypotension and AV block.

Dobutaine or Exercise Stress Echo

This modality has the advantage of no radiation exposure but is very dependent on sonographer and imaging cardiologist experience. The accuracy may be negatively impacted by patient habitus and acoustic window.

Positron Emission Tomography

PET scan is costly and has limited availability. However, the predictive accuracy may be a little better than SPECT and there is lower radiation dose.

Computed Tomography Coronary Angiography

This is an established noninvasive method for evaluating coronary anatomy and myocardial function. Studies have demonstrated that computed tomography coronary angiography (CTCA) has a high diagnostic accuracy for detecting the presence of coronary artery stenosis.⁷¹ Severe calcification can impact the specificity of CTCA to evaluate coronary artery disease, however the use of subtraction CTCA has been shown to improve specificity when compared to conventional CTCA, 62.5% vs 85.4%, respectively.⁷²

A study of 239 patients undergoing CTCA before intermediate-risk noncardiac surgery, compared to RCRI and coronary artery calcium (CAC) score, suggested the presence of significant coronary artery stenosis (diameter stenosis $\geq 50\%$) and multivessel CAD on CTCA were the strongest predictors of postoperative cardiac complications.⁷³ In a study of 844 noncardiac surgery patients a screening CTCA found patients with >3 coronary lesions had a risk of perioperative major cardiac events of 14.0% versus 2.2% in patients without significant CTCA findings regardless of RCRI score.⁷⁴ The sensitivity, specificity, positive predictive, and negative predictive values were 76%, 73%, 8%, and 99%, respectively.⁷⁴ A recent meta-analysis with eleven studies included evaluating the use of CTCA in risk stratification prior to noncardiac surgery found that the severity and extent of CAD on CTCA conferred incremental risk for perioperative MACE with multivessel disease having the greatest risk (23.1% perioperative MACE versus only 2% of patients with no CAD).⁷⁵

One of the most exciting developments in noninvasive preoperative evaluation of the vascular surgery patient is the availability of Fractional Flow Reserve CTCA (FFRCT).^{76,77} The results of FFRCT correlates with findings on invasive fractional flow reserve but does not require invasive placement of a pressure wire across the suspected lesion to obtain trans-stenotic pressure gradient response to intracoronary vasodilator.⁷⁸ Since invasive FFR is a great predictor of future cardiac events, this less invasive approach has obvious potential advantages for perioperative evaluation (lesion location, severity and hemodynamic significance).⁷⁹ We anticipate this evolving technology will play an increasingly important role in preoperative cardiac risk assessment in the near-term future.

PREOPERATIVE CORONARY ANGIOGRAPHY AND REVASCULARIZATION

The decision to proceed to coronary angiography based on the noninvasive testing depends on an assessment of whether the benefits of an intervention outweigh the risks associated with the intervention and delaying surgery. Earlier retrospective studies suggested that preoperative coronary revascularization in vascular surgery patients was associated with better postoperative and long-term survival.^{80,81} However, these studies were limited by their retrospective design and failure to include all patients who died or had serious complications from the preoperative revascularization. The 2004 randomized Coronary Artery Prophylaxis (CARP) trial (which included 510 candidates for major vascular surgery) failed to show benefit from preemptive cardiac revascularization. The CARP trial included a minority of patients with severe ischemia on noninvasive testing and excluded patients with left main disease and severely reduced LVEF, yet still dramatically changed how we approach our vascular patients.⁸² Monaco and associates randomized 208 consecutive open AAA patients with RCRI ≥ 2 to either a “selective strategy” with coronary angiography only if their stress test was positive or a “systematic strategy” with routine screening coronary angiography.⁸³ This small study supports the concept of preoperative screening coronary angiography for open AAA surgery but was not adequately powered to influence current guidelines. A retrospective study evaluating 1104 patients who underwent vascular surgery re-demonstrated that significant CAD predicted an increased risk of mortality and cardiovascular death on follow-up, but also did not demonstrate a difference in the overall mortality between the patients who had coronary revascularization and those who did not.⁸⁴ Presently, revascularization before noncardiac surgery is recommended in circumstances in which revascularization is indicated according to existing clinical practice guidelines (Class I, Level of Evidence C). It is not recommended that routine coronary revascularization be performed before noncardiac surgery exclusively to reduce perioperative cardiac events (Class III, Level of Evidence B).⁴⁷ An algorithm for guiding preoperative cardiac imaging and revascularization in vascular surgery patients is presented (see Chapter Algorithm 2). Note that we rely

on the multidiscipline vascular team to balance the risk:benefit of preoperative coronary revascularization based on burden of myocardial ischemia, potential delay of surgery due to needed antiplatelet therapy, risk of cardiac revascularization and complexity of the planned surgical procedure.

BEST MEDICAL THERAPY TO REDUCE PERIOPERATIVE CARDIAC COMPLICATIONS

Beta Blockade

It seems intuitive that harnessing the adrenergic system and decreasing the myocardial oxygen consumption during and after surgery would have a beneficial effect on reducing the risk of type II MI. However, subsequent studies showed the cardiovascular benefit of beta-blockers was counterbalanced by a significant increase in stroke and all-cause mortality.^{85–88} Continuation of beta-blockers in the 25% of patients on pre-procedure therapy is currently the only Class I beta-blocker indication for vascular surgery (Class 1 Level B).^{25,89} It may be reasonable to initiate beta-blockers (atenolol or bisoprolol preferred) with preoperative titration in high-risk patients based on Level IIa supporting evidence.

Statins

Many studies have demonstrated the positive impact of statins on outcomes of patients undergoing vascular surgery. Patients taking statins at the time of infrainguinal bypass, lower extremity endovascular therapy, carotid endarterectomy and open aortic aneurysm repair have been demonstrated to have decreased mortality compared to patients not on statins^{90–94} (see Ch. 13, Hyperlipidemia). The use of statins has been demonstrated to positively impact patients' long-term outcome after vascular surgery; however, in-hospital outcomes are less clear. A study utilizing the Vascular Quality Initiative (VQI), including more than 14,000 patients who underwent major vascular surgery, found no association between the rate of in-hospital MI/death and the preoperative use of antiplatelet agents or statins but the study was limited by the registry design.⁹⁵ A meta-analysis including randomized controlled trials (675 patients) and observational studies (22,861 patients) found perioperative statin use was associated with a significantly lower risk of all-cause mortality, MI, stroke, and the composite of MI, stroke, and death; however, there was no significant impact on cardiovascular mortality.⁹⁶ Based on current evidence perioperative continuation of statins is recommended and long half-life or extended-release formulations are favored (Class 1, Level C). Preoperative initiation of statin therapy should be considered in patients undergoing vascular surgery, ideally at least 2 weeks before surgery (Class IIa Level B).⁶³

Aspirin

While the benefit of primary prevention of major cardiovascular events in patients without clinical cardiovascular disease is

offset by bleeding,⁹⁷ the utility of aspirin as secondary prevention is well established in high-risk patients⁹⁸ (see Ch. 42, Antiplatelet Agents). In the perioperative setting, the large-scale POISE-2 RCT (10,010 noncardiac surgery patients with 6% undergoing vascular surgery) showed that aspirin given before surgery and throughout the early postsurgical period had no effect on composite death or nonfatal MI but increased the risk of major bleeding.⁹⁹ In a POISE-2 substudy of patients who had vascular surgery (603 patients), it was demonstrated that perioperative withdrawal of aspirin did not increase cardiovascular or vascular occlusive complications.¹⁰⁰ Among vascular surgery patients, the ACE (Aspirin and Carotid Endarterectomy) randomized trial compared four doses of aspirin in patients having carotid endarterectomy (CEA) and found that the combined risk of stroke, MI, and death at 30 days and 3 months after endarterectomy was lower for patients taking 81 mg or 325 mg aspirin daily than for those taking higher doses of aspirin (650 mg and 1300 mg).¹⁰¹ Unfortunately, the ACE trial did not have a placebo control. Another prospective nonrandomized two-arm comparative study in patients undergoing CEA showed that the overall cardiac and neurologic complication rate was lower in the aspirin group compared with the group not on aspirin (5.2% vs. 17.6%, respectively), with no significant increase of postoperative bleeding necessitating revision.¹⁰²

Currently it is unclear in patients undergoing vascular surgery if aspirin should be continued or withdrawn for surgery. There does appear to be at least moderate evidence that aspirin should be continued for patients undergoing carotid endarterectomy and it is important to note the POISE-2 trial excluded patients undergoing CEA.⁹⁹ The Canadian perioperative guidelines suggest not starting aspirin or continuing aspirin in patients undergoing noncardiac surgery; however, in patients who undergo CEA or have a recent coronary artery stent, aspirin may be continued.³⁴ The ACC/AHA guidelines also do not recommend initiation or continuation of aspirin in patients undergoing elective noncardiac or noncarotid surgery, who have not had previous coronary stenting (Class III Level B), unless the risk of ischemic events outweighs the risk of surgical bleeding Class III Level C).⁴⁷ The ESC/ESA guidelines do not take a strong stance and recommendations are based on individual risk assessment: (1) discontinuation of aspirin therapy, in patients previously treated with it, should be considered in those in whom hemostasis is anticipated to be difficult to control during surgery (Class IIa Level B); (2) continuation of aspirin, in patients previously treated, may be considered in the perioperative period, and should be based on an individual decision that depends on the perioperative bleeding risk, weighed against the risk of thrombotic complications (Class IIb Level B).²⁵

Dual Antiplatelet Therapy After Coronary Stenting

More than 1 million PCI procedures are conducted annually in North America alone, and more than 5% of these patients will undergo elective surgery within 1 year.¹⁰³ The availability

of drug-eluting stents significantly reduced the need for repeat intervention by reduction of in-stent neointimal proliferation (restenosis). However, this came with the trade-off of delayed healing, leaving the patient vulnerable to stent thrombosis with discontinuation of dual antiplatelet therapy (DAPT).¹⁰⁴ The decision on when to discontinue in DAPT requires a multidisciplinary approach with the risk of stent thrombosis being adjudicated based on the location, type of stent, associated burden of myocardium at risk, stent diameter and lesion length/complexity, and most importantly the time interval between stent placement and the needed surgery.¹⁰⁵ However, based on current guidelines a simplified algorithm is provided (see Chapter Algorithm 3).¹⁰⁶ Further detail on DAPT management in this setting can be found in the 2018 second Stent and Surgery Consensus statement (SAS-2).¹⁰⁷

INTRAOPERATIVE VARIABLES IMPACTING MACE

The pre-emptive intraoperative challenge is to reduce the demand for oxygen of “at risk” myocardium and at the same time maintain or increase the supply of oxygen to the tissue.¹⁰⁸ There are technical aspects of the surgery that directly impact the ability of the intraoperative team to maintain hemodynamic stability and optimize surgical outcome. This section focuses on the non-technical aspects of intraoperative management that can impact the risk for cardiac complications.

Type of Anesthetic Technique and Agent Utilized

The type of anesthesia used for a vascular operation can potentially impact cardiovascular risk and the ability to perform the planned procedure. There are four main classifications of anesthesia that can be employed: local anesthesia, regional anesthesia (including peripheral nerve blockade and neuraxial blockade), monitored anesthesia care (MAC; intravenous sedation with or without local anesthesia), and general anesthesia (which can include volatile-agent anesthesia, total intravenous anesthesia, or a combination of both).⁴⁷ The use of neuraxial versus general anesthesia for noncardiac surgery has not been proven to decrease the risk of MI.^{53,109} The use of volatile anesthetic agents have been demonstrated to decrease mortality and complications in cardiac surgery patients^{110,111}; however, in noncardiac patients volatile anesthetic agents do not positively impact mortality or risk of myocardial ischemia.^{110,112} The benefit of volatile anesthetic in coronary artery bypass grafting (CABG) has even been recently challenged by a multi-center, single-blind, controlled trial that showed no difference in 1-year mortality or 30-day composite of nonfatal MI or death when compared to intravenous anesthesia.¹¹³ The use of volatile anesthetics vs. total intravenous anesthesia was evaluated in a prospective randomized trial in patients undergoing abdominal aortic surgery and there was no difference in the myocardial injury occurrence on the first postoperative day between the two treatment groups.¹¹⁴ The ACC/AHA guidelines

for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery issued a recommendation (IIa LOE A) that the use of either a volatile anesthetic agent or total intravenous anesthesia is reasonable for patients undergoing noncardiac surgery.⁴⁷

The use of neuraxial anesthesia can decrease postoperative pain-induced sympathetic nervous system activation and reduce resultant plasma catecholamine increase.¹¹⁵ Higher postoperative pain scores are associated with an increased risk of myocardial injury in patients undergoing noncardiac surgery.¹¹⁶ Importantly, a Cochrane Review of 15 trials comparing open abdominal aortic surgery using epidural pain relief versus systemic opioid-based pain relief demonstrated that epidural analgesia provided better pain management than systemic opioids and it significantly reduces the risk of MI, time to tracheal extubation, postoperative respiratory failure, gastrointestinal bleeding, and intensive care unit length of stay compared to systemic opioids.¹¹⁷ Practice guidelines from the American Pain Society for management of postoperative pain recommended that clinicians offer neuraxial analgesia for major thoracic and abdominal procedures, especially in patients at risk for cardiac complications, pulmonary complications, or prolonged ileus with a strong recommendation and high-quality evidence.¹¹⁸ The ACC/AHA guidelines for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery states that neuraxial anesthesia for postoperative pain relief can be effective in patients undergoing abdominal aortic surgery to decrease the incidence of perioperative MI (IIa LOE B).⁵³ It should be noted that this recommendation was not echoed in the Society for Vascular Surgery (SVS) practice guidelines on care of patient with an abdominal aortic aneurysm, citing insufficient evidence to support either the intraoperative or postoperative use of epidural anesthesia although the Cochrane Review was not referenced.¹¹⁹

Intraoperative Blood Loss and Transfusion

Anemia requiring transfusion has been associated with increased mortality in patients undergoing percutaneous coronary intervention (PCI)¹²⁰ and noncardiac surgery (general, vascular, and orthopedic surgery).¹²¹ The need for perioperative blood transfusion in patients undergoing vascular surgery increases the 30-day risk of myocardial infarction (3.3- to 8-fold), cardiovascular events (5.0-fold increase), and the risk of all-cause mortality (4.4- to 11.7-fold increase).¹²²⁻¹²⁴ Interestingly, increased MI was seen only in postoperative transfusion but not intraoperative transfusion in a study evaluating 3689 patients undergoing open major vascular surgery.¹²⁵ The higher risk associated with postoperative transfusions may, in part, be related to ongoing bleeding, shock or reflect inadequate transfusion/resuscitation during the operation.

Transfusion of allogeneic RBCs does confer specific risks including volume overload, bacterial contamination, blood-borne pathogens, transfusion-related acute lung injury, and acute transfusion reactions.^{126,127} There is no prospective data to confirm intraoperative cell salvage positively impacts mortality or MACE. However, the evidence that cell salvage

diminishes the need for allogeneic blood transfusion led the SVS to recommend the use of intraoperative cell salvage or an ultrafiltration device if a large blood loss is anticipated during abdominal aortic aneurysm repair (Level 1 Recommendation, Quality of Evidence B).¹¹⁹ If intraoperative cell salvage is used, it is important to recognize that there is a significant reduction of coagulation factor concentrations/activities by the washing process and this needs to be considered for adequate management of coagulation during the operation.¹²⁸

Intraoperative Blood Pressure Management

Intraoperative BP is manipulated via fluid management as well as pressor infusion when warranted. The reported incidence of intraoperative hypotension can range from 5%–99% in noncardiac surgery depending on the chosen definition used to delineate low BP.¹²⁹ Increased intraoperative BP variability in noncardiac surgery has been associated with an increased 30-day mortality.^{130,131} However in a study by Maheshwari et al., increased BP variability did not appear to be as important of a predictor of mortality as low intraoperative mean arterial pressure.¹³² Intraoperative hypotension is associated with an increased risk of myocardial injury and death as well as increased risk of acute kidney injury.^{130,133–136} In a large retrospective cohort analysis of 57,315 patients undergoing noncardiac surgery both a relative 20% decrease of intraoperative MAP or an intraoperative MAP below 65 mm Hg were associated with an increased postoperative risk of myocardial injury and acute kidney injury. A large multicenter cohort study that enrolled 16,079 patients evaluated the association of intraoperative heart rate (HR) and systolic BP in noncardiac surgery (VISION Study).¹³⁶ In this study, intraoperative tachycardia (HR >100 beats per minute [bpm]) was associated with increased risk of myocardial injury, myocardial infarction, and 30-day mortality; however, intraoperative hypotension (SBP <100 mm Hg) was associated with increased risk of myocardial injury and 30-day mortality but not myocardial infarction.¹³⁶ The VISION Trial also demonstrated SBP >160 mm Hg to be associated with an increased risk of myocardial injury and myocardial infarction but with a reduced risk of mortality. Furthermore, a HR <55 bpm was associated with a reduced risk of myocardial injury, myocardial infarction, and mortality. The highest risk of myocardial injury occurred when the patient had a combination of an SBP <100 mm Hg and an HR >100 bpm¹³⁶ (see Ch. 35, Intraoperative Management). A study evaluating the impact of intraoperative hypotension on 890 vascular surgery patients aged 60 years or older undergoing general anesthesia or a combination of regional and general anesthesia found 29% of patients with intraoperative hypotension (MAP <60 mm Hg) had postoperative myocardial injury compared to 20% of patients without intraoperative hypotension ($P = 0.001$).¹³⁷ After adjustment for potential confounding factors, a 40% decrease from the pre-induction MAP with a cumulative duration of more than 30 minutes was associated with an increased risk of postoperative myocardial injury.¹³⁷

A consensus statement published in the *British Journal of Anaesthesia* discussing intraoperative blood pressure, risk, and

outcomes for elective surgery was published in 2019.¹³⁸ Two consensus statements were established that apply to noncardiac surgery: (1) Intraoperative mean arterial pressures below 60–70 mm Hg are associated with myocardial injury, acute kidney injury, and death. Injury is a function of hypotension severity and duration. (2) For adult noncardiac surgical patients, there is insufficient evidence to recommend a general upper limit of arterial pressure at which therapy should be initiated, although pressures above 160 mm Hg have been associated with myocardial injury and infarction.

Hypothermia

Surgery places a patient at risk for hypothermia (core body temperature <36°C) secondary to patient exposure, cold environment, evaporation from within surgical incisions, and exposure to unwarmed intravenous fluids combined with an impairment of normal autonomic thermoregulatory control from general anesthesia.¹³⁹ Hypothermia during surgery has been demonstrated in trials to increase blood loss, increase the risk for transfusion, and increase the risk of wound infection.^{140,141} However it is not clear if intraoperative hypothermia is associated with an increased risk of myocardial injury and myocardial infarction. A trial of 300 patients undergoing abdominal, thoracic, or vascular surgical procedures with documented CAD or who were at high risk for CAD were randomized to receive either hypothermic or normothermic care. The trial demonstrated that normothermic patients had a 55% reduction in risk of cardiac events (unstable angina/ischemia, cardiac arrest, or MI) than hypothermic patients.¹⁴² Conversely in a study randomizing patients undergoing cerebral aneurysm surgery to intraoperative hypothermia or normothermia it was demonstrated that there was no significant increase in the occurrence of cardiovascular events in the hypothermic patients.¹⁴³ A retrospective cohort analysis of 2210 patients undergoing noncardiac surgery with general anesthesia also demonstrated no association of mild hypothermia with myocardial injury; though the range of intraoperative temperatures were small and most patients studied were in the normothermic range.¹⁴⁴

Hypothermia in patients undergoing abdominal aortic aneurysm (AAA) repair does seem to impact outcome as patients with a temperature of <36°C on arrival to the recovery room had decreased cardiac output, thrombocytopenia, elevated prothrombin time, inferior Acute Physiology and Chronic health Evaluation (APACHE) II scores, more ST segment changes, and ventricular tachycardia.¹⁴⁵ Bush et al. performed a retrospective analysis of 262 elective AAA repairs and found that patients with hypothermia (measured by core temperature immediately after surgery) had significantly higher APACHE scores and greater fluid, vasopressor, transfusion, and inotropic requirements. Also hypothermic patients had higher incidences of organ dysfunction, prolonged length of stay in the intensive care unit, prolonged length of stay in the hospital, and death.¹⁴⁶

Given the heterogeneity of outcomes in the literature it is not surprising there is some differences in the guidelines regarding intraoperative temperature management. The ACC/

AHA guidelines are less committal to maintenance of normothermia during surgery and state: maintenance of normothermia may be reasonable to reduce perioperative cardiac events in patients undergoing noncardiac surgery (Level IIb LOE B).⁴⁷ The SVS guidelines for the care of a patient with an AAA recommend maintaining core body temperature at or above 36°C during aneurysm repair (Level I LOE A).¹¹⁹

POSTOPERATIVE MANAGEMENT OF CARDIAC COMPLICATIONS

Following major vascular surgery, patients can experience extremes of early physiologic and hemodynamic changes as paroxysms in adrenergic tone are incited by unmasked pain from the receding anesthesia, as well as volume shifts, reperfusion effects, acid–base changes, and normal systemic inflammatory responses (see Ch. 36, Postoperative Management). During this early storm of activity, it can be difficult to recognize a smoldering cardiac complication that is being caused by, or participating in, the hemodynamic changes. If a patient remains on ventilator support this further complicates recognition of early postoperative cardiac events since the patient is not aware of or cannot communicate symptoms. All of these factors contribute to the explanation of why high-risk vascular surgery patients have a high rate of silent ischemia, silent myocardial injury, and infarction, all of which are associated with higher in-hospital, 30-day and 1-year mortality.^{20,22,147–150} Both silent (low levels of cTn) and overt cardiac complications (higher levels of cTn) are strongly linked to poor outcome and both types can precipitate each other.¹⁵¹ There should be a high index of suspicion for silent cardiac complications following major vascular surgery and there should be a low threshold for obtaining an ECG and cTn levels. Indeed, the Canadian perioperative guidelines recommend routine postoperative cTn in all major-risk surgeries.³⁴ Remember, the presence of *ST-segment elevation* is a medical emergency, and an interventional cardiologist must be consulted for possible immediate percutaneous transluminal coronary angioplasty and stenting with a goal of first ECG showing ST elevation to reperfusion of ≤ 60 minutes.¹⁵² Patients who are < 6 months from implantation of a drug-eluting stent (DES) are particularly vulnerable to abrupt stent closure due to DAPT withdrawal and, when possible, should be followed with a multidiscipline team (including interventional cardiology) throughout the entire perioperative period.

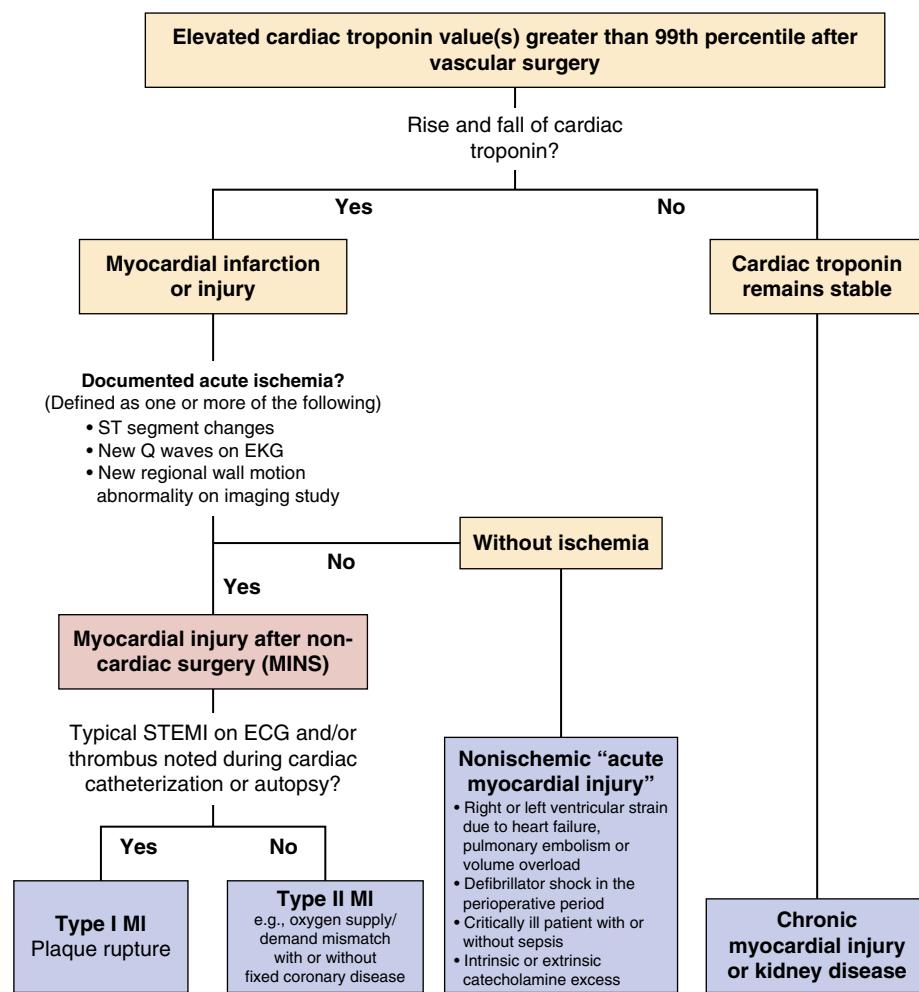
As detailed above, type II MIs are much more common after vascular surgery and if suspected these patients should receive goal-directed medical therapy to enhance oxygen supply

and reduce demand. Supplemental oxygen should be used if the oxygen saturation is $< 90\%$ or if the patient has other high-risk features for hypoxemia.¹⁵³ The treatment of tachycardia and hypertension can be achieved with beta-blockers, calcium channel blockers or analgesics (excluding nonsteroidal anti-inflammatory drugs).¹⁵³ In contrast, treatment of tachycardia associated with hypotension is particularly challenging and requires an objective quantification of volume status, consideration of active bleeding or sepsis and understanding of the patient's baseline and postoperative myocardial, valvular, and coronary physiology. These patients will often require additional diagnostic tests, invasive monitoring, bedside echocardiography, and point-of-care ultrasound assessment. Frequently, vasopressors to maintain blood pressure and beta-blockers to slow heart rate while fine-tuning blood volume, postoperative pain, and respiratory function are necessary. Management of patients with ischemia in the face of hypotension and hypoperfusion is often challenging, and the assistance of an intensive care unit team and consultation with anesthesiologists, intensivists, and cardiologists is warranted. The outcomes of patients who have a cardiac arrest after vascular surgery are very poor and often reflect the spiral described in Figure 44.1. These patients frequently die in spite of receiving CPR and those who survive are likely facing long hospitalization and significant morbidity.¹⁵⁴

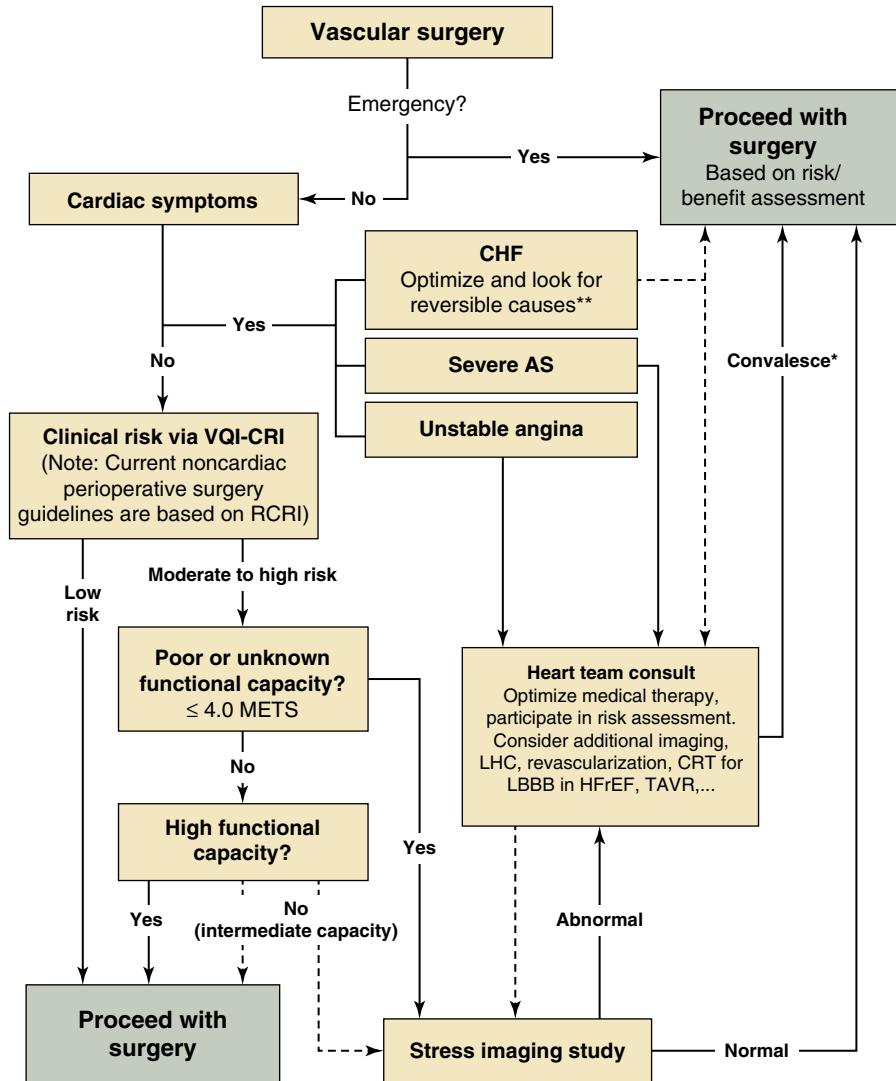
Postoperative CHF is often part of the CAD continuum since the most common cause of baseline poor LV function in high-risk surgical patients is ischemic heart disease and those without known LV dysfunction are most likely to have experienced a perioperative cardiac ischemic event.¹⁵⁵ The presentation of heart failure may be atypical in the context of the postoperative dynamic changes as detailed above.²⁵ Patients with baseline HFrEF are particularly vulnerable to intraoperative volume overload and once the LV dilates they can begin down the spiral detailed in Figure 44.1 with multiple compounding substrates for progressive myocardial injury. These patients need to have meticulous invasive monitoring, judicious use of volume replacement intraoperatively and a multidiscipline team observing them through their recovery. Some of the postoperative heart failure complications in HFrEF patients with EF $\leq 35\%$ and a left bundle branch block with a QRS duration ≥ 120 ms may be reduced by pre-surgical implantation of a cardiac resynchronization defibrillator.^{25,156} In general, postoperative heart failure is managed similar to nonsurgical decompensated CHF and may be aided by assessment of natriuretic peptides. Unfortunately, the long-term prognosis for patients with postoperative CHF is poor and enlisting heart failure team support early during recovery is prudent.¹⁵⁶

CHAPTER ALGORITHMS

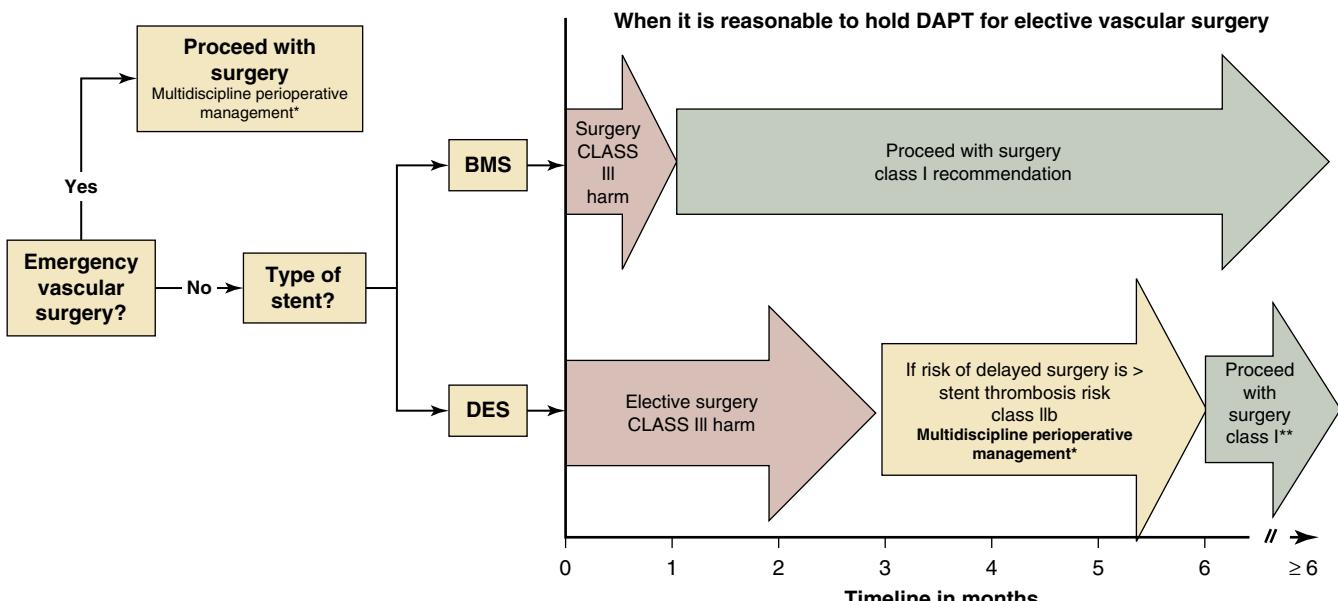
ALGORITHM 1



ALGORITHM 2



ALGORITHM 3

Open vascular surgery timing after coronary stent

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Systemic Complications: Respiratory

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INTRODUCTION	577
PREOPERATIVE RISK STRATIFICATION	577
Patient-Related Risk Factors	577
Procedure-Related Risk Factors	578
Laboratory Test Risk Factors	579
Pulmonary Risk Indices	579
PERIOPERATIVE RISK REDUCTION	580
Preoperative Risk Reduction	580
Intraoperative Risk Reduction	581
Postoperative Risk Reduction	581
CLINICAL MANIFESTATIONS	582
Atelectasis	582
Bronchospasm	582
Pneumonia	582
Acute Respiratory Failure	583
Acute Respiratory Distress Syndrome	583
Transfusion-Related Acute Lung Injury	584
MANAGEMENT STRATEGIES	584
High-Flow Nasal Oxygen	584
Noninvasive Positive Pressure Ventilation	585
Mechanical Ventilation	585
Adjuncts to Mechanical Ventilation	585

INTRODUCTION

Perioperative respiratory complications are significant contributors to morbidity and mortality, occurring in a large percentage of surgical patients.^{1–5} Prevention and effective management of respiratory complications are vital to provide quality patient care, improve outcomes, and minimize healthcare costs.^{1–3} Common perioperative pulmonary complications (Box 45.1) include atelectasis, aspiration pneumonitis, pneumonia, bronchospasm, acute respiratory distress syndrome (ARDS), respiratory failure, pulmonary embolism, and pleural effusion.^{1–3} Patients undergoing vascular surgery in particular are at high risk for these adverse events. This chapter delineates preoperative risk stratification, perioperative risk reduction, clinical manifestations, and management strategies for respiratory complications.

PREOPERATIVE RISK STRATIFICATION

Assessing preoperative risk for respiratory complications requires analysis of patient-related risk factors, procedure-related risk factors, and laboratory test risk factors (Table 45.1). Pulmonary risk indices may also provide insight on preoperative patient optimization.

Patient-Related Risk Factors

Patient factors conferring high risk of developing respiratory complications in patients undergoing noncardiac surgery include advanced age, American Society of Anesthesiology (ASA) score ≥2, smoking history, male gender, obesity, obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and asthma.^{1–3,6–9} A smoking history is known to increase the risk of pulmonary complications by nearly 2.5 times.^{10,11} A systematic review of 9354 studies, including 107 in a meta-analysis, found that the risk of postoperative respiratory complications was 73% higher among smokers than non-smokers.¹¹ Older patients have anatomical changes to the lung parenchyma and chest wall that lead to increased work of breathing and diminished gas exchange. In combination with complex comorbidities and hemodynamic changes, this can cause increased atelectasis and suboptimal ventilation and oxygenation.¹

The physiology of obesity leads to reduced lung volumes, impaired ability to clear secretions, and decreased air flow. Specifically, as BMI increases, functional residual capacity and residual volume decrease. Thus, obese patients are 4.5 times more likely to suffer from respiratory complications.¹ A related disease is obstructive sleep apnea (OSA), which has been

BOX 45.1**Common Postoperative Respiratory Complications**

- Acute lung injury
- ARDS
- Aspiration/aspiration pneumonitis
- Atelectasis
- Bronchitis and tracheobronchitis
- Bronchospasm
- Exacerbation of chronic disease (e.g., chronic obstructive pulmonary disease)
- Healthcare-associated pneumonia (including hospital-acquired and ventilator-associated pneumonia)
- Hypoventilation (from analgesia or residual neuromuscular blockade)
- Pleural effusion
- Pneumothorax
- Pulmonary edema
- Pulmonary embolism
- Respiratory failure (ventilator dependence 48 hours after surgery)
- TRALI
- Upper airway obstruction

ARDS, acute respiratory distress syndrome; TRALI, transfusion-related acute lung injury.

TABLE 45.1**Patient-Related, Procedure-Related, and Laboratory Test Risk Factors for Postoperative Pulmonary Complications**

Patient-Related Risk Factors	Procedure-Related Risk Factors
<ul style="list-style-type: none"> • Advanced age • Functional dependence • ASA Class II or greater • COPD • CHF • Smoking/cigarette use • Poorly controlled asthma • Upper respiratory infection (during previous month) • OSA 	<ul style="list-style-type: none"> • Surgery type (endovascular vs. open) • Surgical site • Duration of surgery 2 hours or longer • Upper abdominal or intrathoracic surgery • Type of anesthesia • Endotracheal intubation • Long-acting neuromuscular blockade • Perioperative blood transfusion • Emergency surgery
Laboratory Test Risk Factors	
<ul style="list-style-type: none"> • Oxyhemoglobin saturation by pulse oximetry ($\text{SpO}_2 < 90\%$) • Albumin $< 35 \text{ g/L}$ • Blood urea nitrogen $> 21 \text{ mg/dL}$ • Anemia (preoperative hemoglobin $\le 10 \text{ g/dL}$) 	

ASA, American Society of Anesthesiologists; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

shown by numerous studies to be an independent risk factor for postoperative respiratory complications.^{10,12–17} The prevalence of OSA is higher in surgical patients compared with the general population and most of these patients are undiagnosed at the time of operation. Perioperatively, patients with OSA have an increased incidence of adverse events including oxygen desaturations, respiratory failure, and reintubation.¹⁷ The use of opiates, sedatives, and anesthetics in the perioperative period are thought to decrease arousal, increase pharyngeal collapse, and impair ventilation.¹⁴ A meta-analysis analyzing 13 studies, comprising 3942 patients, found that patients with OSA had higher incidence of desaturations, respiratory failure,

and ICU transfers.¹³ Other studies found a 2-fold increase in pulmonary complications and mechanical ventilation in OSA patients.^{15,16} Preoperative treatment with continuous positive airway pressure (CPAP) has been shown in some studies to be associated with lower risk of cardiopulmonary complications compared with untreated patients.^{18,19} Thus, guidelines suggest that preoperative use of CPAP should be considered in OSA patients.²⁰

Obstructive lung diseases including chronic obstructive pulmonary disease (COPD) and asthma cause impaired lung function and therefore confer increased risk for postoperative pulmonary complications.^{1,4,7,21–25} In patients undergoing aortic surgery, 40% of those with COPD suffer a respiratory complication.²¹ COPD is associated with increased adverse events and decreased long-term survival in EVAR patients. A study of 3979 patients undergoing elective endovascular aneurysm repair (EVAR) found that COPD was a preexisting condition more common in those requiring prolonged intubation.⁴ In patients with untreated asthma, the incidence of postoperative pulmonary complications is 24%.² This number is reduced to 4.5% in those receiving perioperative systemic corticosteroids. A study of 48,218 patients showed that patients who were hospitalized for asthma in the 3 months prior to an operation had nearly 3 times the risk of contracting postoperative pneumonia.²⁶ Thus, it is worth considering postponement of surgery in patients with recent exacerbations of asthma or COPD until symptoms have resolved and pulmonary function has returned to baseline.^{7,23} Overall, patient-related risk factors should be carefully considered and modified as able in the preoperative period.

Procedure-Related Risk Factors

Risk factors for pulmonary complications related to the procedure itself include type of operation, surgical site, duration of surgery, anesthesia factors, transfusion requirements, and urgency of surgery. Many studies have shown that vascular surgery, in particular aortic surgery, places patients at elevated risk from pulmonary complications compared with other types of surgery.^{3,8,27} In an analysis of 52,562 vascular surgery patients from the Vascular Quality Initiative, there was a 5.4% incidence of postoperative respiratory adverse events.²⁷ Of those, certain vascular operations had the highest rates of pulmonary complications: open abdominal aortic aneurysm repair (17.6%), in situ suprainguinal bypass (9.68%), and thoracic endovascular aortic repair (TEVAR) (9.6%). A study on ARDS showed that 16% of patients undergoing aortic surgery developed acute lung injury.^{28,29} Surgical approach for aortic aneurysm repair has been investigated as a possible variable in respiratory complication rates. In 3530 elective open abdominal aortic aneurysm repair cases, there was no difference in pulmonary complications between retroperitoneal and transperitoneal approaches.³⁰ When comparing open repair with EVAR of 446 ruptured abdominal aortic aneurysms, respiratory complications were more common after open repair (40.5% vs. 25%).³¹ Surgical site, namely proximity of the incision to the diaphragm, is an important risk factor for postoperative

pulmonary complications as well. Upper abdominal and thoracic operations decrease mobility of the diaphragm and therefore reduce ventilation.^{2,3}

Operative duration longer than 2 hours is an important predictor of pulmonary complications.^{1,2,8} Thus, it is wise to be cognizant of case length both during the operation itself and in surgical planning. Anesthesia considerations such as neuromuscular blockade, opioid use, and general anesthesia are risk factors for pulmonary complications.³² These factors cause impaired ability to cough and swallow as well as diminished muscular contraction. Secretions can accumulate, gastric contents are more likely to be aspirated, and lung ventilation is reduced. Some studies have suggested that reversal of neuromuscular blockade with sugammadex or neostigmine may reduce postoperative pulmonary morbidity.^{32–35} There have been conflicting reports of the impact of anesthesia types on vascular postsurgical pulmonary complications. In EVAR patients, one study found that only 0.72% of patients receiving local or regional anesthesia developed respiratory complications and the authors suggest that avoiding general anesthesia may be beneficial.⁴ Separate studies of 8141 and 6009 EVAR patients both found that general anesthesia was associated with more respiratory complications and higher pulmonary morbidity than spinal or local anesthesia.^{36,37} However, a recent study of 9783 elective EVAR patients showed similar frequency of pulmonary complications in general, regional, and local anesthetic groups.³⁸ Another analysis of 16,052 patients undergoing lower extremity bypass showed no significant difference in pulmonary complications between regional and general anesthesia.³⁹

Blood transfusion intraoperatively, as an indicator of hemodynamic instability, has been associated with increased rates of early re-intubation.⁴⁰ In an analysis of 941,496 operative cases, transfusion of just one unit of packed red blood cells increased pulmonary and other complications.⁴¹ Another study of 10,100 patients undergoing vascular, general, and orthopedic operations showed similar results, with those receiving one or two units of blood more likely to have pulmonary complications (OR 1.76).⁴² Urgent and emergent procedures confer exceptionally high risk of respiratory complications.^{27,28} Patients who require emergent procedures have advanced disease pathologies and do not have the option of preoperative optimization for preexisting conditions. In vascular cases, emergent procedures have a pulmonary complication incidence of 25.9%.²⁷ While some of these procedure-related risk factors may not be modifiable, it is important to recognize them and provide prompt and effective management.

Laboratory Test Risk Factors

Although not a substitute for clinical evaluation, certain laboratory studies may be helpful in determining perioperative pulmonary risk. Several studies have shown low preoperative arterial oxygen saturation and anemia (hemoglobin <10 g/dL) to be predictors of pulmonary complications.^{6,43–45} In fact, SpO₂ on room air in supine position was the strongest patient-related risk factor for postoperative respiratory complications.⁴⁴ Preoperative anemia confers almost a 3-fold risk increase for these

complications. Blood urea nitrogen levels greater than 21 mg/dL and albumin less than 35 g/L are also risk factors.⁴⁶

Other tests such as pulmonary function tests (PFTs), arterial blood gas measurements (ABG), chest radiographs (CXR), and exercise testing may be relevant in certain cases, but should not be considered routine. The role of PFTs in preoperative risk stratification is not well established. Most studies indicate that PFTs do not independently predict postoperative pulmonary complications.^{46–48} Patients with COPD or asthma may benefit from PFTs to help optimize clinical status. Similarly, chest radiographs are commonly ordered in the preoperative setting, but rarely influence preoperative management.⁴⁹ A meta-analysis found that only 10% of routine preoperative chest radiographs had abnormalities. Of these, only 1.3% were unexpected and 0.1% resulted in management changes.⁵⁰ Guidelines indicate that it is reasonable to consider chest radiograph in patients with existing cardiopulmonary disease and those older than 50 years undergoing high risk surgery.⁴⁶ There is no data to suggest that hypercapnia or hypoxemia, as identified by ABG, provide prediction of postoperative pulmonary morbidity.

Pulmonary Risk Indices

There have been numerous pulmonary risk indices developed to stratify and predict likelihood of postsurgical respiratory complications.⁴⁹ One well-respected tool is the ARISCAT score, developed from 2464 patients in Spanish hospitals.⁴⁴ It uses four patient-related factors (preoperative SpO₂, recent respiratory tract infection, age, hemoglobin level) and three procedure-related factors (intrathoracic or upper abdominal surgery, procedural length, and emergency surgery) to determine risk of postoperative pulmonary complications (Table 45.2).⁴⁴ The ARISCAT score has subsequently been externally validated in the PERISCOPE study across 63 European centers spanning 21 countries.⁴³ The SLIP model analyzed 4366 patients for postoperative acute lung injury and classified them into low, intermediate, and high risk. The predictors were cardiac, vascular, or thoracic surgery, diabetes mellitus, COPD, GERD, and alcohol abuse.⁵¹ In patients with baseline risk factors for ARDS, the SLIP-2 model was found to perform better and identified nine predictive characteristics: aortic surgery, cardiac surgery, sepsis, emergency surgery, cirrhosis, admission location other than at home, increased respiratory rate, FiO₂ greater than 35%, and SpO₂ less than 95%.⁵²

Another risk index, SPORC, took the following factors into account: ASA ≥3, emergency procedure, high risk surgery, COPD, and congestive heart failure. A score of 0 conferred a 0.12% risk of reintubation, while scores of 7–11 had a 5.9% risk of reintubation.⁵³ The SPORC-2 index added seven intraoperative factors to predict respiratory complications.⁴⁰ The LAS VEGAS score also took intraoperative factors into account. This index showed independent association between postoperative pulmonary complications and six patient-related factors (age, ASA score, anemia, SpO₂, OSA, active cancer), two procedure-related factors (emergency procedure, surgical length), and five intraoperative characteristics (airways other

TABLE 45.2**Prediction of Postoperative Pulmonary Complications**

Preoperative Predictor	Odds Ratio (95% CI)	Point Value
Age (years)		
≤50	1	—
51–80	1.4 (0.6–3.3)	3
>80	5.1 (1.9–13.3)	16
Preoperative SpO₂ (%)		
≥96	1	—
91–95	2.2 (1.2–4.2)	8
≤90	10.7 (4.1–28.1)	24
Respiratory infection in last month		
Preoperative anemia ($\leq 10\text{ g/dL}$)	3.0 (1.4–6.5)	11
Surgical Incision		
Peripheral	1	—
Upper abdominal	4.4 (2.3–8.5)	15
Intrathoracic	11.4 (4.9–26.0)	24
Duration of Surgery (hours)		
≤2	1	—
>2–3	4.9 (2.4–10.1)	16
>3	9.7 (4.7–19.9)	23
Emergency surgery	2.2 (1.0–4.5)	8
Class	Point Total	Predicted Probability of Postoperative Pulmonary Complication (%)
Low risk	<26	1.6 (0.6–2.6)
Intermediate risk	26–44	13.3 (7.6–19.0)
High risk	>45	42.1 (29.3–54.9)

CI, Confidence interval; SpO₂, oxyhemoglobin saturation by pulse oximetry breathing room air in supine position.

Modified from Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort.

Anesthesiology. 2010;113:1338–1350.

than supraglottic, IV anesthetic with volatile agents, desaturations, high PEEP, and vasopressor use).⁶ Gupta et al. formulated two calculators using the NSQIP dataset, one for evaluating respiratory failure and one for predicting pneumonia.^{54,55} Finally, the Arozullah respiratory failure index examined 81,719 men at 44 VA medical centers.⁵⁶ It stratifies patients into five classes of risk based on surgical type, urgency of procedure, albumin level, BUN level, functional status, age, and COPD. These are all tools that can be used in conjunction with clinical assessment to estimate surgical risk.

PERIOPERATIVE RISK REDUCTION

Some of the aforementioned risk factors for pulmonary complications are modifiable. Care should be taken preoperatively,

intraoperatively, and postoperatively to minimize risk and ensure optimal patient outcomes.

Preoperative Risk Reduction

Patient optimization preoperatively is important to help prevent respiratory complications. Measures such as smoking cessation, nutritional supplementation, pulmonary rehabilitation including respiratory muscle training, chest physiotherapy, and incentive spirometry have all been suggested as methods to reduce risk.⁵⁷ Patients should be encouraged to quit smoking as soon as possible prior to surgical intervention. One study of 1962 patients over 60 years old undergoing noncardiac surgery showed that current smokers and those who quit within 93 days of surgery had increased risk of postoperative pulmonary complications compared with nonsmokers. However, smokers who quit more than 93 days preoperatively did not show increased risk.⁵⁸ Several other studies have found variable lengths of time necessary for reducing complications associated with smoking. A systemic review and meta-analysis showed that at least 4 weeks of smoking cessation is required to decrease respiratory complications.⁵⁹ Less than 4 weeks neither increases nor decreases respiratory complication rates. Taken together, surgeons should advise patients to cease smoking as early as possible, with the knowledge that a longer period of cessation is more effective in reducing risk.

Preoperative education to inform patients of mobility and breathing exercises has been reported to confer a 75% relative risk reduction and 20% absolute risk reduction for pulmonary complications.⁶⁰ A randomized controlled trial of 441 patients within 6 weeks of elective open upper abdominal surgery was conducted to compare pulmonary outcomes after a preoperative information booklet versus a 30 minute physiotherapy session.^{60,61} The incidence of pulmonary complications in the intervention group was significantly lower than the control group (12% vs. 27%), with an absolute risk reduction of 15%.⁶⁰ This trial suggests that preoperative breathing exercises may be a useful method to decrease pulmonary morbidity. Similarly, a Cochrane review including 12 trials of patients undergoing elective cardiac and major abdominal surgery found that preoperative inspiratory muscle training reduced rates of postoperative atelectasis and pneumonia.⁶²

Patients with comorbidities such as OSA, COPD, and asthma should be medically optimized prior to surgery as they would be in nonoperative settings. Treatments for patients with obstructive airway disease may include pneumococcal and influenza vaccines, bronchodilators, leukotriene antagonists, steroids, oxygen, and potentially noninvasive positive pressure ventilation (NIPPV).^{1,63} A small study of 30 COPD patients with greater than 40 pack years undergoing aortic surgery showed lower rates of pulmonary complications in those starting NIPPV at home 2 weeks preoperatively.^{21,23} Patients with both asthma and COPD should avoid environmental triggers preoperatively. If respiratory infections or fluid and electrolyte imbalances occur, they should be appropriately treated.⁶³ Preoperative pulmonary rehabilitation and

correction of malnutrition also play important roles. Patients with OSA should be instructed to adhere to CPAP use prior to surgery.^{64,65}

Intraoperative Risk Reduction

There are numerous intraoperative factors that influence development of pulmonary complications, many of which are difficult to modify. When feasible, the risks and benefits of endovascular techniques should be considered as an alternative to open procedures. There are some data to suggest that endovascular approaches are associated with fewer respiratory complications compared with open approaches.^{31,66–69} However, surgeon assessments of individual cases and risk–benefit analysis are more discerning than a general recommendation.^{70,71}

Lung protective ventilation has been investigated as a measure to prevent postoperative pulmonary complications with conflicting results. In the randomized controlled PROVHILO trial, 900 patients were enrolled to receive either high PEEP of 12 cm H₂O with recruitment maneuvers or low PEEP ≤2 cm H₂O without recruitment maneuvers. Pulmonary complications occurred in 40% of the higher PEEP group and 39% of the lower PEEP group, indicating no benefit of lung protective ventilation as utilized in this trial. In another trial, 1012 patients undergoing abdominal surgery were randomized to one of four ventilation strategies and found that overall pulmonary complications were not reduced with protective ventilation.⁷² However, a meta-analysis of randomized trials found that adjusting ventilatory settings intraoperatively with the aim of minimizing lung injury had a significant effect on reducing pulmonary complications. The included studies used a PEEP of at least 5 cm H₂O with a tidal volume ≤8 mL/kg predicted body weight and intermittent recruitment maneuvers.⁷³ An expert consensus panel recommends an individualized ventilation plan initially set to a tidal volume of 6–8 mL/kg predicted body weight with a PEEP of 5 cm H₂O. Thereafter, the PEEP should be individualized. When recruitment maneuvers are used, they should be performed for the shortest time at the lowest pressure.⁷⁴

Additionally, goal-directed fluid therapy without use of vasoactive agents was shown to reduce pulmonary complications.⁷³ In the FEDORA trial, 450 patients undergoing major elective surgery were given fluids intraoperatively either following traditional principles or based on goal-directed hemodynamic therapy. The parameters included maintenance of maximal stroke volume, MAP>70 mm Hg, cardiac index ≥2.5 L/min per m². The patients receiving goal-directed fluids had fewer cases of pulmonary edema, ARDS, and pneumonia.⁷⁵ Use of neuromuscular blocking agents has been shown to increase risk of respiratory complications.^{73,76} High doses of neuromuscular blocking agents were found to confer greater risk than low doses.⁷⁷ There is some evidence that appropriate reversal with neostigmine or sugammadex reduces this risk.^{33,78–80} A recent randomized trial compared sugammadex with neostigmine and found a trend toward reduced pulmonary complications using sugammadex, but no significant difference between the two agents.^{79,81}

Postoperative Risk Reduction

Risk reduction postoperatively should emphasize early extubation, increasing lung expansion, optimal analgesic techniques, preventing aspiration, and giving appropriate nutrition. Ventilator associated pneumonia (VAP) occurs in 9%–27% of intubated patients, causing increased mortality and longer ICU stays.⁸² Limiting duration of intubation is the most important factor in preventing VAP. The risk of VAP is 3% per day during the first 5 days of ventilation and 2% per day from days 5 to 10, with half of all VAP cases occurring within the first 4 days.^{83,84} VAP prevention bundles include measures such as head of bed elevation, daily sedation interruption, oral care with chlorhexidine, orotracheal route of intubation, closed endotracheal suctioning systems, and hand hygiene.^{57,82–87}

Most pneumonia prevention programs have targeted intubated ICU patients and not necessarily patients on surgical wards. Accordingly, there have been a few major studies that investigate protocols to decrease rates of pneumonia in a postoperative patient population. In these protocols, there is a focus on lung expansion modalities combined with multifaceted levels of care. One study analyzed a VA population of patients on the surgical wards who received noncardiac surgery. An intervention protocol was established that included 8 steps: nursing staff education, cough and deep breathing exercises using an incentive spirometer, oral hygiene twice daily with chlorhexidine, ambulation, head of bed elevation, discussion of progress with staff, pneumonia bundle documentation, and a computerized order set in the medical records.⁸⁵ Prior to intervention, 13 of 1668 patients were diagnosed with pneumonia (0.78%). After intervention, 3 of 1651 patients were diagnosed with pneumonia (0.18%). This represents an 81% overall decline in pneumonia rates over an 18 month period.⁸⁵ A 5-year follow-up study using the same preventative protocol found a 43.6% decrease in pneumonia compared to the preintervention rate.⁸⁸ Another study, the I COUGH trial, implemented a similar program in general and vascular surgery patients that includes incentive spirometry, cough and deep breathing, oral hygiene, patient education, ambulation, pain control and head of bed elevation.⁸⁹ After starting this program, postoperative pneumonia rates fell from 2.6% to 1.6% and unplanned reintubation rates decreased from 2% to 1.2%.⁸⁹

There is insufficient evidence that specific lung expansion modalities reduce risk when used alone.⁹⁰ A Cochrane review demonstrated no adequate evidence that incentive spirometry prevents pulmonary complications after upper abdominal surgery.^{91,92} Noninvasive ventilation methods such as CPAP are thought to improve atelectasis and limit need for reintubation.⁵⁷ A small study of 182 patients received five 30-minute noninvasive ventilation sessions during the first 2 days postoperatively. The incidence of pulmonary complications was lower in the intervention group (7% vs. 18%).⁹³ However, a Cochrane review evaluating 10 studies concluded there is insufficient evidence to state the benefit or harm of using CPAP in patients postoperatively.^{7,94,95} In obese patients specifically, a meta-analysis found that perioperative noninvasive ventilation reduced respiratory complications overall and therefore may be of benefit.⁹⁶ A multicenter randomized controlled trial

to evaluate the effectiveness of perioperative CPAP in patients over 50 years undergoing major abdominal surgery has been conducted with results pending.⁹⁷ Finally, the OPERA trial, including 220 post-surgical patients, showed that high-flow nasal cannula did not improve pulmonary outcomes compared with standard oxygen therapy.⁹⁸

Post-surgical analgesia is another area of management that can affect respiratory complications.⁵⁷ Epidural analgesia has been found to decrease the risk of postoperative pulmonary complications compared with opioid use alone.^{7,99} In patients with COPD, epidural analgesia is particularly beneficial to improve respiratory ability.^{100,101} A meta-analysis of 125 trials with 9044 patients found that epidural analgesia decreased the rates of respiratory depression, pneumonia, and atelectasis.¹⁰² Multimodal analgesia should be encouraged to minimize use of systemic opioids.⁶⁴

Nasogastric decompression in the postoperative period should be used selectively for symptom relief and certain surgical indications. Patients are 5 to 8 times more likely to develop a pulmonary complication after undergoing abdominal surgery if a nasogastric tube is used.^{7,103} Routine nasogastric tube use has no benefit and is associated with higher rates of atelectasis and pneumonia.^{104,105} Malnutrition confers greater pulmonary complication risk. However, routine parenteral nutrition does not reduce this risk. Nutritional status should be monitored clinically and using laboratory values to ensure adequate supplementation. Early oral feeding is encouraged to restore bowel function and maintain gut mucosal integrity.^{90,106,107}

CLINICAL MANIFESTATIONS

Atelectasis

Atelectasis is characterized by collapse or filling of alveoli with fluid and foam causing reversible loss of aerated lung.¹⁰⁸ It causes impairment of oxygenation, reduced lung compliance, elevated pulmonary vascular resistance, tissue injury, and can serve as a focus of infection.^{108,109} Up to 90% of all patients undergoing anesthesia have atelectasis, with a maximum decrease in functional residual capacity (FRC) within the first few minutes of a general anesthetic.¹⁰⁹ More than 15%–20% of the lung can be collapsed prior to surgery, accounting for an FRC reduction of 20%–30%.¹⁰⁸ Atelectasis occurs after both IV and inhalational anesthesia, whether the patient is breathing spontaneously or paralyzed. There are multiple mechanisms that cause atelectasis including anesthetic-induced surfactant inhibition, mechanical compression of lung tissue from diaphragmatic displacement, loss of respiratory muscle function, and changes in oxygen tension. Intraoperative ventilatory management using low tidal volume and PEEP and postoperative techniques such as adequate pain control may be beneficial in decreasing volume of atelectatic lung.^{110,111} Although it is widely thought that atelectasis can cause postoperative fever, there is little evidence to demonstrate this association and incentive spirometry has not been shown to be effective at preventing fever.^{92,112,113}

Bronchospasm

Bronchospasm is caused by contraction of bronchial smooth muscle leading to increased work of breathing, impaired airflow, air trapping, dynamic hyperinflation, and ventilation-perfusion mismatch.¹¹⁴ Although the incidence of intraoperative bronchospasm is low, it can cause life-threatening hypoxemia and hypercarbia, especially in patients with asthma.^{114–116} Bronchospasm can be provoked by mechanical stimuli such as tracheal intubation and extubation, laryngoscopy, suctioning, aspiration, trauma, and surgical manipulation. Medications can trigger bronchospasm through histamine release, muscarinic activity, or allergic reactions. Other aggravating factors include patient pain and anxiety. Signs of bronchospasm are elevated peak inspiratory pressure, prolonged expiratory phase, and lack of chest fall. Management includes use of short-acting beta-2 selective agonists, IV corticosteroids, and IV epinephrine. Anticholinergic agents, magnesium, antiemetics, and gastric suctioning are adjunctive therapies that may be used as well. Adequate control of asthma preoperatively is the most effective method for preventing bronchospasm.^{114–116}

Pneumonia

Pneumonia is an acute infection of the lung parenchyma caused by microorganisms such as bacteria, viruses, and fungi.¹¹⁷ Among hospital-acquired infections, pneumonia is the most common and causes significant morbidity and likely mortality.¹¹⁸ Guidelines from the Infectious Diseases Society of America and the American Thoracic Society categorize pneumonia as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Previously defined healthcare-associated pneumonia (HCAP) is no longer included in the most recent guidelines due to new evidence that patients with HCAP are not at high risk of multidrug resistance organisms. Likewise, community-acquired pneumonia (CAP) should be treated as a separate category due to differing causative organisms. HAP is defined as a pneumonia occurring 48 hours or more after hospital admission that was not incubating at time of admission. VAP occurs greater than 48 hours after endotracheal intubation specifically.

The etiology of VAP is associated with microaspiration of contaminated secretions and bacterial colonization of the oropharynx.¹¹⁹ The most common pathogens causing VAP are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter spp.*, *Proteus spp.*, *Escherichia coli*, *Klebsiella spp.*, and *Hemophilus influenzae*.¹²⁰ Multidrug-resistant organisms have been isolated with high frequency in cases of VAP, with one study identifying methicillin resistance in 55.7% of *S. aureus* infections.^{119,120} Many cases are also caused by polymicrobial infection. There may be considerable variation in pathogen distribution among different institutions and clinicians should be aware of specific pathogens and antibiotic sensitivities within their institution, and even in specific ICUs.

Diagnosis of VAP is challenging due to nonspecific clinical findings. It is generally agreed that pneumonia can be defined by new or persistent pulmonary infiltrates along with clinical

TABLE 45.3 Clinical Pulmonary Infection Score for Ventilator-Associated Pneumonia

	0 Points	1 Point	2 Points
Temperature (°C)	36.5–38.4	38.5–38.9	≤36.0 or ≥39
Peripheral WBC	4000–11,000	<4000 or >11,000	<4000 or >11,000 and >50% bands
Tracheal secretions	None	Nonpurulent	Purulent
Pulmonary radiography	No infiltrate	Diffuse/patchy infiltrates	Localized infiltrate
Culture of ET suction	No growth	Heavy growth	Heavy growth and positive Gram stain
Oxygenation ($\text{PaO}_2/\text{FiO}_2$)	>240 or ARDS		≤240 and no ARDS

CPIS Score >6 is consistent with ventilator-associated pneumonia.

ARDS, acute respiratory distress syndrome; ET, endotracheal tube; FiO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of oxygen in arterial blood; WBC, white blood cell count in cells/cubic milliliter of blood.

Modified from Pugin J, Auckenthaler R, Mili N, Janssens J, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1991;143:1121–1129.

signs of an infectious origin. These signs may include fever, purulent secretions, leukocytosis, and decreased oxygenation.¹¹⁸ Guidelines indicate that noninvasive respiratory sampling, i.e. endotracheal aspiration, is preferable to invasive techniques such as bronchoalveolar lavage for diagnostic purposes, though there is considerable debate about this point and great institutional variation. The clinical pulmonary infection score (CPIS) is a diagnostic tool that evaluates several parameters including temperature, white blood cell count, tracheal secretion characteristics, oxygenation, chest X-ray, and tracheal aspirate cultures. A score of greater than 6 confers a high likelihood of pneumonia (Table 45.3).^{121–123} Although CPIS may be useful for diagnosis, guidelines suggest that clinical criteria alone be used in decisions regarding antibiotic treatment.

Treatment of VAP should be guided by individual hospital generated antibiograms in order to target specific pathogens as narrowly as possible. The guiding principles are to adequately treat while limiting superfluous coverage and to de-escalate when appropriate.¹¹⁸ Empiric treatment of VAP should include coverage for *S. aureus*, *P. aeruginosa*, and other Gram-negative bacilli. MRSA coverage with vancomycin or linezolid should be added only in patients with a risk factor for antimicrobial resistance, patients in units where greater than 10%–20% of *S. aureus* isolates are methicillin resistant, or patients in units where prevalence is unknown. Risk factors for antimicrobial resistance include prior IV antibiotic use within 90 days, septic shock, ARDS, hospitalization for 5 or more days prior to VAP diagnosis, and acute renal replacement therapy prior to VAP diagnosis. Guidelines also suggest dual antipseudomonal coverage in patients with a risk factor for resistance, units in which greater than 10% of Gram-negative isolates are resistant, and units with unknown susceptibility. Recommended treatment duration is generally 7 days.

Acute Respiratory Failure

Acute respiratory failure is caused by an inability to protect the airway, a failure to oxygenate and/or a failure to ventilate. Overall, 5%–10% of surgical patients develop postoperative respiratory failure. Up to 40% of those undergoing abdominal

surgery will develop respiratory failure.¹²⁴ Loss of airway protection may occur due to anesthetics and neuromuscular blocking agents, laryngeal edema, bronchospasm, impaired cough and gag reflexes, and neurological issues. Hypoxemic respiratory failure is characterized by tachypnea with a pO_2 less than 60 mm Hg or a PaO_2 to FiO_2 ratio of less than 300 mm Hg.^{125–128} Etiologies of hypoxemic respiratory failure relate to problems with oxygen diffusion or ventilation–perfusion mismatch in the alveoli. Acute pulmonary edema, pneumonia, sepsis, atelectasis, and pulmonary embolism can all cause hypoxemic respiratory failure.^{124,127} Therefore, using PEEP and increasing FiO_2 can be effective strategies for improvement of oxygenation.

Hypercapnic respiratory failure is defined by a PaCO_2 greater than 50 mm Hg, often causing respiratory acidosis with a pH less than 7.35.^{129,130} Generally, a reduction in alveolar ventilation or increase in physiologic dead space causes hypercapnic respiratory failure. Chronic lung diseases can lead to loss of pulmonary elasticity and tissue stiffening that cause increased work of breathing and decreased ventilation. Post-operative opioid use, residual anesthetic effects, and dysfunction of respiratory muscles may depress respiratory drive and reduce ventilation.^{129,130} Improvements in ventilation via increased tidal volume and respiratory rate should be utilized in hypercapnic respiratory failure. The etiology of acute respiratory failure should be identified for appropriate management. Often in the postoperative setting intubation and mechanical ventilation should be considered. In certain situations noninvasive ventilation and/or high-flow oxygen therapy may be appropriate.^{125,126}

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a form of acute diffuse lung injury precipitated by a predisposing risk factor that causes increased pulmonary vascular permeability and decreased functional lung tissue.¹³¹ According to the Berlin definition, the onset of ARDS occurs within 7 days of a known clinical insult or with new or worsening respiratory symptoms.^{131,132} Imaging will show bilateral

TABLE 45.4**The Berlin Definition of Acute Respiratory Distress Syndrome**

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Pulmonary radiography	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation	Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Mild ARDS	$200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}$
Moderate ARDS	$100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$
Severe ARDS	$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$
Mortality	
Mild ARDS	27% (CI 24%–30%)
Moderate ARDS	32% (CI 29%–34%)
Severe ARDS	45% (CI 42%–48%)

ARDS, acute respiratory distress syndrome; CI, 95% confidence interval; CPAP, continuous positive airway pressure; FiO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure.

Modified from ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526–2533.

opacities that cannot be fully explained by pulmonary effusion, atelectasis, or masses. ARDS is stratified into three categories of severity based on $\text{PaO}_2/\text{FiO}_2$ ratio with a minimum PEEP or CPAP of 5 cm H_2O : mild $200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$; moderate $100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$; and severe $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ (Table 45.4).¹³¹ Mortality is 27% in mild ARDS, 32% in moderate ARDS, and 45% in severe ARDS.¹³³

The annual incidence of ARDS in the United States is cited as 75 cases per 100,000 population.^{132,134} A study of 29,144 patients showed that 10% of ICU patients and 23% of those mechanically ventilated were diagnosed with ARDS.^{132,135} There is a high mortality associated with ARDS and patients who survive often have complications including cognitive impairment, post-traumatic stress disorder, muscle weakness, and depression. Conditions that predispose patients to developing ARDS include pneumonia, aspiration, pulmonary contusion, inhalation injury, drowning, sepsis, trauma, hemorrhagic shock, pancreatitis, burn, drug overdose, transfusion, cardiopulmonary bypass, and reperfusion injury.¹³² The pathogenesis of ARDS proceeds in several phases. The exudative phase begins with immune cell damage of alveolar endothelial and epithelial barrier function leading to inflammation and accumulation of protein rich fluid. In proliferative phase, edema is reabsorbed and alveolar architecture, and therefore function, is re-established. The fibrotic phase results from basement membrane damage and inability to repair alveolar epithelium. This phase does not occur in all patients and is associated with

increased mortality rates and prolonged mechanical ventilation.¹³² Management strategies for ARDS will be discussed below.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a clinical syndrome of respiratory compromise including dyspnea, hypoxemia, hypotension, fever, and pulmonary edema occurring after blood transfusion.¹³⁶ The pathophysiology of TRALI is thought to result from a two-hit hypothesis where the underlying proinflammatory condition of the patient provides the first hit and the transfusion provides the second hit.^{137,138} TRALI has been recently redefined into two types based on patients with and without risk factors for ARDS.^{139,140} TRALI type I can be diagnosed with the following criteria: no risk factors for ARDS, hypoxemia with $\text{PaO}_2/\text{FiO}_2 \leq 300$ or $\text{SpO}_2 < 90\%$ on room air, bilateral pulmonary edema on imaging, no contribution of left atrial hypertension, and onset within 6 hours of transfusion. TRALI type 2 is diagnosed in patients with risk factors for ARDS, a stable respiratory status in the 12 hours prior to transfusion, and otherwise the same specifications as type I.¹³⁹ Recognition and expeditious diagnosis of TRALI is vital to institute adequate treatment and prevent morbidity. TRALI is estimated to occur once in every 5000 transfusions and is a leading cause of transfusion-related death, with a mortality of 5%–10%. In one series, all patients required oxygen support and 72% required mechanical ventilation. However, when identified and treated properly, most patients have resolution of symptoms and excellent long-term prognosis.^{136,141,142}

MANAGEMENT STRATEGIES

A number of different noninvasive and invasive strategies may be used for management of perioperative pulmonary complications.

High-Flow Nasal Oxygen

High-flow nasal oxygen (HFNO) has emerged as an effective therapy for management of hypoxemia and acute respiratory failure in the postoperative setting. HFNO delivers fully humidified and heated gas via nasal prongs at a rate of 20 to 60 L/minute, allowing for an FiO_2 of 21 to 100%.^{143,144} Studies suggest that HFNO improves oxygenation and reduces dyspnea via several mechanisms: pharyngeal dead space washout, decreased work of breathing, generation of positive end-expiratory pressure, increased mucociliary clearance, lowering metabolic cost for gas conditioning, and decreased airway resistance.^{143,144} Advantages of HFNO include enhanced patient comfort, ease of implementation, low nurse workload, ability to eat and communicate during therapy, and therefore increased patient compliance. It is important for clinicians to closely monitor patients on HFNO to avoid an increased risk of delayed intubation.

There have been several trials investigating the effectiveness of HFNO post-extubation. One trial included 527

mechanically ventilated ICU patients, 251 of which were post-surgical, and randomized them to receive HFNO or conventional oxygen therapy post-extubation.^{143,145} Re-intubation rates within 72 hours were lower in the HFNO group (4.9% vs. 12.2%). Another study randomized 604 high risk ICU patients (232 postsurgical) to receive HFNO or non-invasive ventilation for 24 hours after extubation.¹⁴⁶ HFNO was found to be noninferior to noninvasive ventilation for preventing reintubation and respiratory failure. Finally, the OPERA trial randomized 220 patients undergoing major abdominal surgery at moderate to high risk of postoperative pulmonary complications to HFNO or standard oxygen therapy after extubation. There was no significant difference found in postoperative pulmonary complications between the two groups.⁹⁸ HFNO is a promising therapy, but there are still unanswered questions in terms of patient selection, optimal timing of treatment, and determination of treatment escalation.

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NPPV) refers to delivery of positive pressure to the lungs via oronasal airways using a facemask, helmet, or nasal cannula.¹⁴⁷ In continuous positive airway pressure (CPAP), patients breathe through a pressurized circuit against a resistor that is able to provide constant pressure during inspiration and expiration.^{148,149} Bilevel NPPV provides different levels of support during the inspiratory and expiratory phases. NPPV reduces work of breathing, reopens atelectatic alveoli, improves gas exchange, redistributes extravascular fluids, and increases functional residual capacity.^{127,147–151} Use of NPPV has been shown to effectively prevent and treat respiratory failure.¹⁵¹ NPPV is considered standard treatment for COPD exacerbation and is associated with improved survival in multiple conditions such as pulmonary edema, and acute respiratory failure.^{127,147} One randomized controlled trial examined patients who developed severe hypoxemia after major elective abdominal surgery. Patients received either standard oxygen or oxygen in addition to CPAP. The CPAP group had a ten-fold lower intubation rate in addition to lower rates of pneumonia, infection, and sepsis. The trial was ended early due to efficacy after 209 patients were enrolled.¹⁴⁸ A second trial had similar results, analyzing 293 patients undergoing abdominal surgery who developed hypoxic respiratory failure. These patients were randomized to standard oxygen therapy or NPPV. Those receiving NPPV had significantly lower incidence of reintubation (33.1% vs. 45.5%), fewer healthcare-associated infections, and greater number of ventilator-free days.^{151,152} A Cochrane review found two studies comparing NPPV versus standard oxygen therapy for treatment of acute respiratory failure after upper abdominal surgery and found that NPPV reduced rates of intubation, pneumonia, sepsis, and wound infection. NPPV was also effective in decreasing ICU length of stay and improving blood gases and pH one hour after intervention.¹⁴⁹ Although risks of gastric distention and aspiration exist when using NPPV, overall it is an effective, safe therapy and avoids injuries associated with endotracheal intubation. A patient failing NPPV

should be identified early and provided with endotracheal intubation and mechanical ventilation to prevent an increased risk of death if delayed more than 2 hours.

Mechanical Ventilation

Mechanical ventilation is the cornerstone of management for respiratory failure, and in particular ARDS.^{132,153} The goals of mechanical ventilation are to maintain adequate gas exchange and support respiratory muscles while minimizing ventilator-induced lung injury.¹⁵³ Overdistention of the lungs causes volutrauma, cyclical opening and closing of alveoli leads to atelectrauma, and endothelial injury worsens systemic inflammation via biotrauma. Lung protective ventilation is a strategy used to prevent these forms of injury. The landmark ARDS Network trial resulted in clinical practice guidelines recommending low tidal volumes of 4 to 8 mL/kg of predicted body weight, and maintaining a plateau pressure of <30 cm of water.^{154,155} This has been shown to reduce mortality and increase ventilator-free days compared with higher tidal volumes.¹⁵⁶

Guidelines also conditionally recommend using higher PEEP and recruitment maneuvers. However, there is some controversy regarding this recommendation. A Cochrane review of 10 trials found that ventilation strategies including recruitment maneuvers had no effect on 28-day or hospital mortality.¹⁵⁷ A meta-analysis of 2299 patients with acute lung injury showed that the subgroup of those with ARDS had a relative reduction in mortality of 10% when receiving higher levels of PEEP.¹⁵⁸ Another meta-analysis found no significant benefit of higher PEEP in terms of mortality, barotrauma, organ failure, or ventilator-free days.¹⁵⁹ The EPVent2 trial investigated outcomes using esophageal pressure guided PEEP versus empirical high PEEP-FiO₂ and found no difference.¹⁶⁰ Notably, the recent ART trial included 1010 ICU patients with moderate to severe ARDS and compared a control strategy of low PEEP with an experimental strategy of lung recruitment in addition to PEEP titration. The experimental strategy increased 28-day mortality, 6-month mortality, risk of barotrauma, and need for vasopressors in the first hour. This trial was published after most recent guidelines were instituted and suggests uncertainty in optimal management.¹⁶¹

High-frequency oscillatory ventilation (HFOV) delivers very small tidal volumes at high mean airway pressures and has been investigated as a method for ARDS management. However, a composite of six randomized controlled trials, including the OSCAR trial, showed no difference in mortality.^{155,162} The OSCILLATE trial reported higher mortality with HFOV.¹⁶³ Therefore, routine use of HFOV is not recommended.

Adjuncts to Mechanical Ventilation

A number of adjunctive therapies have been examined and used in concert with mechanical ventilation for management of ARDS and respiratory failure. Guidelines recommend prone positioning of patients with severe ARDS for more than 12 hours per day.^{153,155} The PROSEVA trial enrolled 466 patients with severe ARDS and randomized into groups receiving prone

positioning for at least 16 hours per day or supine positioning.¹⁶⁴ Both 28-day (16% vs. 32.8%) and 90-day (23.6% vs. 41%) mortality were significantly lower in the prone group. Prone positioning is thought to reduce ventilator-associated lung injury via more uniform distribution of tidal volume, changes in chest wall mechanics, and decreasing compression of the left lower lobe by the heart.¹³² Enhancement in oxygenation is achieved by improving ventilation–perfusion mismatch and increasing lung recruitment.¹⁵⁵ Although proning confers a higher risk of endotracheal tube obstruction and pressure sores, the rates of these complications are low and can be minimized with a trained team.¹⁶⁵

The efficacy of neuromuscular blockade in improving ARDS outcomes is controversial. The randomized controlled ACURASYS trial was conducted in 2010 and found that administration of a 48-hour infusion of cisatracurium decreased mortality in patients with moderate to severe ARDS.¹⁶⁶ It is thought that neuromuscular blockade promotes patient-ventilator synchrony and limits reverse triggering, thus reducing ventilator-associated lung injury.^{132,153} The recently published ROSE trial randomized 1006 patients with moderate to severe ARDS to receive 48-hour continuous cisatracurium with deep sedation versus no neuromuscular blockade with lighter sedation. This study, in contrast, found no difference in 90-day mortality.¹⁶⁷ Notably, the ROSE trial used light sedation in the control group while the ACURASYS trial used deep sedation in both experimental groups. It remains unclear what role neuromuscular blockade plays in the management of ARDS.

There is no consensus on fluid management strategy in ARDS. A large randomized controlled trial in 2006 showed that a conservative fluid management strategy improved lung function and decreased duration of mechanical ventilation, with no difference in 60-day mortality.¹⁶⁸ However, a more recent study found that different subphenotypes of ARDS respond to fluid differently.¹⁶⁹

Pharmacologic therapies have not been shown to improve mortality in ARDS. Inhaled nitric oxide transiently improves oxygenation, but does not decrease mortality rates and is associated with increased renal impairment.^{132,170} Glucocorticoids, surfactant replacement, neutrophil elastase inhibition, keratinocyte growth factors, anticoagulation, nonsteroidal anti-inflammatory medications, statins, β_2 agonists, and antioxidants have all shown no mortality benefit and have no role in the routine management of ARDS.^{132,153}

Venovenous extracorporeal membrane oxygenation (VV ECMO) should be considered in patients with severe ARDS when other management strategies fail.^{132,171} In the CESAR trial, 180 patients with severe ARDS were randomized to receive conventional management or referral to a center

for consideration of ECMO. Of the patients considered for ECMO, 63% survived to 6 months as opposed to 47% who survived with conventional management.¹⁷² A major criticism of this trial is that not all referred patients were treated with ECMO, making it difficult to draw definite conclusions about the efficacy of ECMO versus optimal treatment of ARDS at a referral center. The recent EOLIA trial allocated patients with severe ARDS to early ECMO or conventional management and found that 60-day mortality was not significantly different between the two groups.¹⁷³ However, 28% of those assigned to the control group crossed over and received salvage ECMO for refractory hypoxemia. A subsequent post-hoc Bayesian analysis showed a high likelihood ECMO resulting in survival benefit.^{174,175} Two meta-analyses found that ECMO is effective in reducing mortality with one study showing that ECMO was the highest-ranking intervention for ARDS.^{176,177} Thus, ECMO may be an important but as yet undefined therapy to use in patients with severe ARDS refractory to other management options.

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Systemic Complications: Renal

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RENAL ANATOMY	587
RENAL FUNCTION	587
Neuroendocrine Modulators of Renal Function	589
Paracrine and Endocrine Modulators of Renal Function	589
RENAL DYSFUNCTION AFTER VASCULAR AND ENDOVASCULAR PROCEDURES	590
General Approach to Patients with Renal Dysfunction	590
Acute Renal Dysfunction: Causes	590
ISCHEMIC INJURY TO THE KIDNEY	591
Acute Ischemic Renal Injury	591
Chronic Ischemia and Ischemic Nephropathy	592

Toxic Injury and Angiography	592
ALTERED RENAL FUNCTION DURING AORTIC SURGERY	595
Fluid Shifts Associated with Aortic Surgery	595
Renal Failure Associated with Aortic Surgery	596
Protection of Renal Function During Aortic Surgery	597
MEDICAL MANAGEMENT OF ACUTE RENAL FAILURE	598
DIALYSIS	599
Ultrafiltration and Hemofiltration	599
Peritoneal Dialysis	600
CHAPTER ALGORITHM	600

Comprehension of renal anatomy and physiology is necessary to understand the complex changes in renal function that can occur during treatment of vascular disorders. This chapter provides a brief summary of renal function and physiology underlying renal complications in the vascular surgical patient population.¹

RENAL ANATOMY

Renal components include nephrons, collecting ducts, and the microvasculature. The human kidney contains approximately 1 million nephrons, which consist of short or long loops of Henle. The long loops extend to the inner medulla and the short loops to either the outer medulla or the cortex. The collecting ducts descend within the medullary rays of the cortex and fuse to form papillary ducts (Fig. 46.1A).

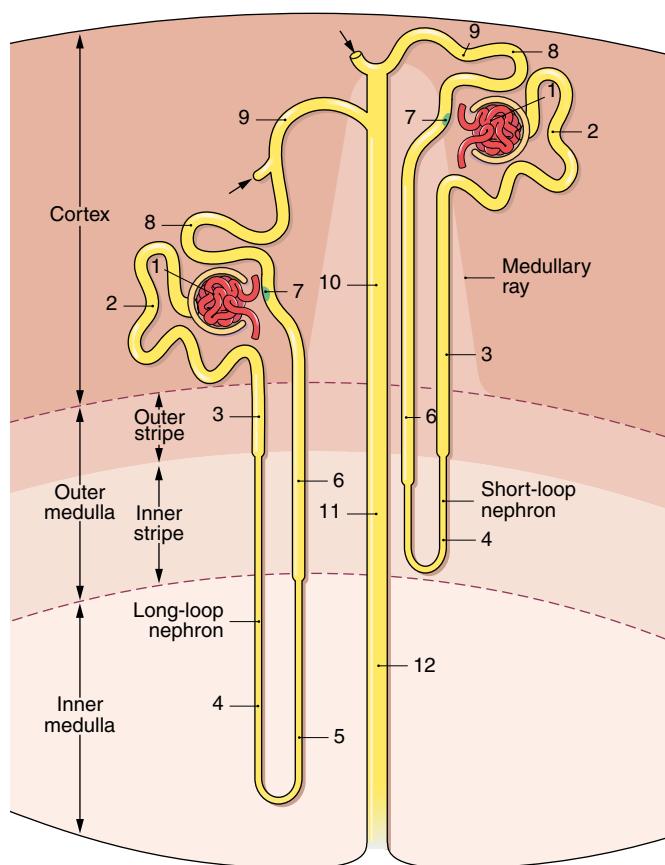
The renal artery divides into the cortical interlobar arteries, which divide into the arcuate arteries at the junction of the cortex and the medulla. These vessels then divide into the cortical radial arteries (none penetrate the medulla) that give rise to the afferent arterioles, which supply the glomeruli. The glomeruli are drained by efferent arterioles that can be cortical or juxtaglomerular. The cortical efferent arterioles are derived from the superficial and midcortical glomeruli and supply the capillary plexus of the cortex. The juxtaglomerular efferent arterioles supply the renal medulla. At the level of the outer stripe of the medulla, the juxtaglomerular efferent arterioles divide into the

descending vasa recta to supply the adjacent medullary plexus. Ascending vasa recta drain the renal medulla. They traverse the outer medulla and form the capillary plexus of the outer stripe and then empty into the arcuate veins.

The microvasculature provides a unique countercurrent exchange between the blood entering and leaving the medulla. The unique vascular anatomy also separates blood flow in the inner stripe from in the inner medulla. The descending vasa recta supplying the inner medulla are not exposed to the tubules of the inner or outer stripe (outer medulla). Blood flow in the ascending vasa recta from the inner medulla and inner stripe perfuses the outer stripe. Venous drainage accompanies the arteries. The arcuate veins drain the cortex and medulla. The arcuate veins join to form the interlobar veins, parallel to the interlobar arteries (see Fig. 46.1A).²

RENAL FUNCTION

The kidney is the major site responsible for maintenance of intravascular volume and composition. The kidney provides three basic physiologic processes: glomerular filtration, selective tubular secretion, and selective tubular reabsorption.^{3,4} The kidney receives a fourth of the cardiac output, approximately 900 L/day of plasma flow. The glomeruli filter 20% of renal plasma flow and must reabsorb 99% of the 180 L of plasma filtered per day to provide a urine output of 1.8 L/day (for a 70-kg man). This ultrafiltrate has the same electrolyte and solute



- A
- | | |
|--|-------------------------------------|
| 1. Renal corpuscle | 7. Macula densa |
| 2. Proximal convoluted tubule | 8. Distal convoluted tubule |
| 3. Proximal straight tubule | 9. Connecting tubule |
| 4. Descending thin limb | 10. Cortical collecting duct |
| 5. Ascending thin limb | 11. Outer medullary collecting duct |
| 6. Distal straight tubule (thick ascending limb) | 12. Inner medullary collecting duct |

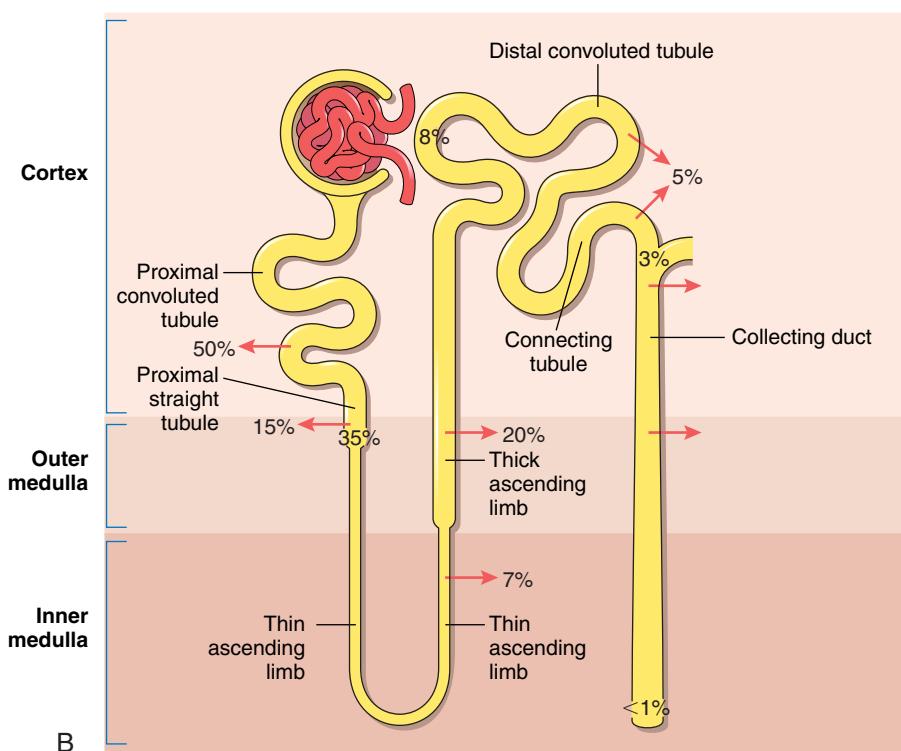


Figure 46.1 (A) Nephrons and the collecting duct system. Short- and long-looped nephrons are shown together with a collecting duct (not drawn to scale). Arrows denote the confluence of further nephrons. (B) Renal sodium handling by the nephron. Figures outside the nephron represent the approximate percentage of the filtered load reabsorbed in each region. Figures within the nephron represent the percentages remaining. (A. Adapted from Shirley DG, et al. Renal physiology. Page 2, A. (Figure 1.2 in Kriz W, et al. Renal anatomy. In: Freedhally J, et al., eds. *Comprehensive Clinical Nephrology*, 6th ed., Philadelphia, PA: Saunders Elsevier; 2019:2). B. Page 20 (Figure 2.7 in Bailey MA, et al. Renal physiology. In: Freedhally J, et al., eds. *Comprehensive Clinical Nephrology*, 6th ed., Philadelphia, PA: Saunders Elsevier; 2019:20.)

concentration as plasma, and is almost totally reabsorbed.⁵ The solute content and volume of urine that enters the renal pelvis are very different compared to the glomerular filtrate. The filtrate flows through the different portions of the tubule, where the solute content and volume are altered by tubular reabsorption and tubular secretion. Solute movement from the tubular lumen to the peritubular capillary plasma is termed tubular reabsorption (tubular secretion is the opposite).

The descending loop of Henle is permeable to water but only minimally permeable to sodium and chloride, whereas the ascending loop is not permeable to water but has active transport mechanisms that readily transport the chloride ion with concomitant passive transport of sodium. This is the underlying basis for the countercurrent mechanisms that produce the medullary osmotic gradient that is important in the regulation of urine osmolarity. Reabsorption of sodium from the distal tubule and from the proximal collecting ducts is controlled by aldosterone secretion. Only 0.2% to 0.8% of sodium is excreted per day of the total sodium filtered (Fig. 46.1B). Potassium is reabsorbed in the proximal convoluted tubule and the thick ascending limb of Henle. Ten percent of the filtered load reaches the early distal tubule. Potassium secretion by connecting cells in the late distal tubule and/or cortical collecting system is variable.^{3–6}

Neuroendocrine Modulators of Renal Function

Intravascular volume is regulated primarily by a series of baroreceptors located in the arterial tree and the atria. These receptors not only sense changes in pressure or volume (atrial receptors) but also monitor the rates of change during the cardiac cycle. Factors that decrease cardiac performance alter intravascular volume and are perceived by these receptors, which then alter renal function to retain salt and water. Similarly, when the concentration of circulating plasma proteins is reduced, there is a net diffusion of intravascular water into the extravascular space secondary to the decreased intravascular oncotic pressure. This net decrease in circulating volume is sensed by these same receptors, and neuroendocrine regulators of urinary output inhibit excretion of water in response. When the baroreceptors perceive a reduction in circulating volume, their afferent signals are reduced, which decreases their tonic inhibition over the neuroendocrine system leading to increased secretion of vasopressin, 13-endorphins growth hormone, adrenocorticotrophic hormone through the central nervous system, and an increased release of adrenal medullary epinephrine. A reduction in arterial pressure or central venous pressure (or both) results in an increase in renal sympathetic nerve stimulation that reduces urinary sodium excretion via three mechanisms: (1) constriction of afferent and efferent arterioles, which reduces renal blood flow and GFR; (2) reabsorption of sodium in the proximal tubule and the thick ascending loop of Henle; and (3) stimulation of renin secretion. Baroreceptors within the macula densa cells of the juxtaglomerular apparatus perceive a decrease in intravascular pressure or plasma ion concentration and stimulate juxtaglomerular cells to release renin. Renin is released in response to increased sympathetic nerve

activity, reduced stretch of the afferent arteriole, and decreased transport of NaCl to the macula densa. Renin catalyzes angiotensinogen to form angiotensin I which is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II induces arteriolar constriction of the afferent and efferent arterioles and thereby causes an increase in blood pressure while decreasing renal blood flow; second, it stimulates renal sodium reabsorption in the proximal tubule; and third, it induces secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Aldosterone secretion results in sodium reabsorption in the distal tubule and collecting duct.^{1–6}

Paracrine and Endocrine Modulators of Renal Function

A number of paracrine and endocrine substances influence renal function. Eicosanoids are a class of vasoactive metabolites of three different enzymes: cyclooxygenase (COX), lipoxygenase, and cytochrome P-450. COX is present as both constitutive (COX-1) and inducible forms (COX-2). Conversion of arachidonic acid to prostaglandins and thromboxane occurs via both enzymes. The major renal eicosanoids are prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2). These potent vasodilators buffer renal vasoconstrictors such as thromboxane A2, angiotensin II, and norepinephrine. Decreased synthesis of the renal vasodilators PGE2 and PGI2 has been associated with renal vasoconstriction in several injuries.^{7–15} PGE2 has been shown to inhibit sodium reabsorption from the thick ascending limb of Henle, and thus contributes to protecting the renal medulla during hypoxia. COX-2 expression has been found in the macula densa and is thought to contribute to release of renin via PGE2. This could be one of the mechanisms responsible for the low renin levels found in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs). The loss of COX-2 expression can also reduce medullary blood flow.

Nitric oxide (NO) is another endogenous renal vasodilator that contributes to the maintenance of normal renal blood flow and function.^{12–22} Zou and Cowley demonstrated NO synthesis in the medulla and the cortex and concluded that NO might play a role in the control of vascular tone and tubular function in the kidney.²³ Loss of endogenous NO synthesis has been suggested to contribute to renal vasoconstriction after renal ischemia-reperfusion injury from either local or systemic causes.^{12,13,16–23} NO is present in the macula densa as the neuronal synthase form (nNOS). Downregulation of nNOS may contribute to arteriolar vasoconstriction by down-regulating COX-2 and subsequent PGE2 synthesis. NO has also been shown to help mediate the increased natriuresis following an increase in renal interstitial hydrostatic pressure.²⁴ Atrial natriuretic peptide (ANP) is released from atrial myocytes after atrial stretch secondary to increased blood volume. ANP increases sodium excretion directly and by down-regulating renin and aldosterone secretion and increases GFR by afferent arteriolar vasodilation.

The kidney is a rich source of endothelins, vasoconstrictor peptides, which function as autocrine and paracrine substances. Endothelin-1 (ET-1) is synthesized in the afferent and

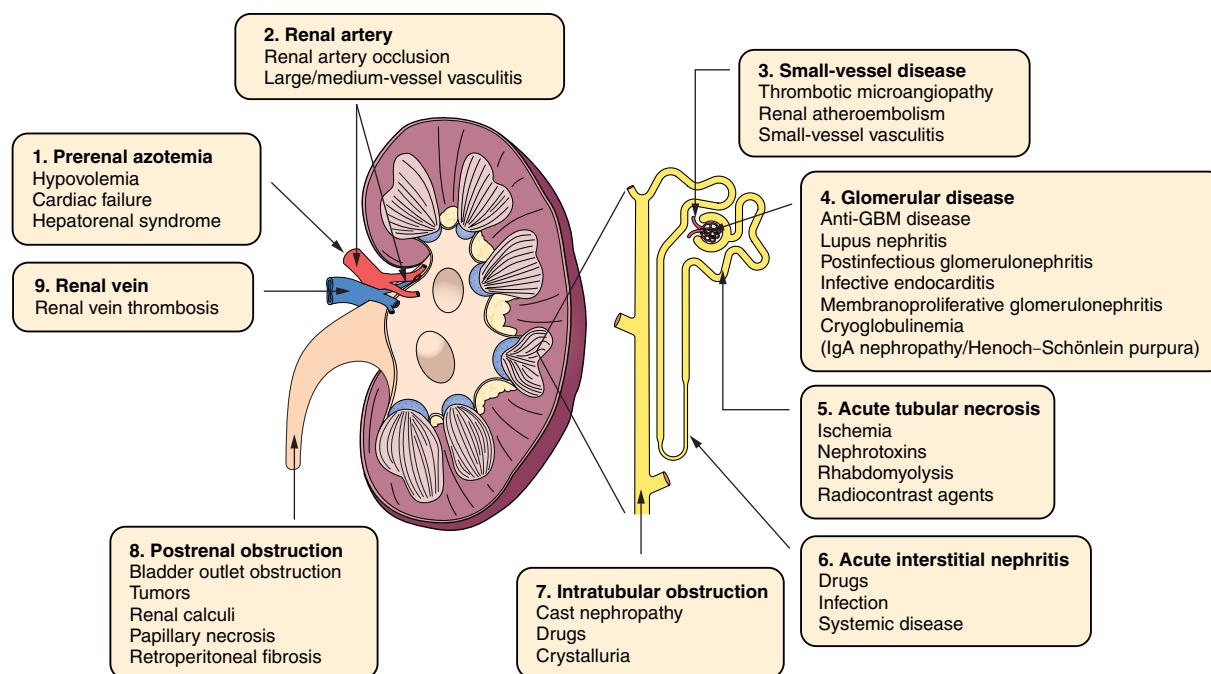


Figure 46.2 Causes of Acute Renal Failure. Acute renal failure is classified into prerenal, renal, and postrenal causes. GBM, glomerular basement membrane; IgA, immunoglobulin A. (Adapted from Figure 66.1, in Haseley and Jefferson JA. Pathophysiology and etiology of acute kidney injury. In: Freehally J, et al. (eds). *Comprehensive Clinical Nephrology*, 6th ed. Philadelphia, PA: Saunders Elsevier; 2019:787.)

efferent arterioles, where it induces vasoconstriction, and in mesangial cells, where it induces contraction. Upregulation of ET-1 synthesis induces a marked reduction in renal blood flow and GFR. ET-1 can inhibit sodium reabsorption in the medullary thick ascending limb, and this may, in part, be mediated by NO. There is recent evidence that ET-1/NO interactions are important in sodium and water excretion.²⁵

Purines are another complex class of autocrine substances that may be involved in renal physiology. Purinoreceptors are divided into P1 and P2 purinergic receptors (P1R, P2R). P1R are upregulated in response to adenosine. P2R are stimulated by nucleotides such as ATP and adenosine diphosphate (ADP). P2 receptors are subdivided into P2XR (there are 7) and P2YR (there are 8) receptors. P1R and P2XR are located in the afferent arteriole and contribute to vasoconstriction. P1R, P2XR, and P2YR are located along the nephron. Endogenous adenosine enhances proximal tubular reabsorption, whereas luminal ADP inhibits it. In the collecting duct, basolateral ATP inhibits vasopressin-sensitive water reabsorption, and basolateral and luminal ATP inhibits sodium reabsorption. There is evidence that uric acid may cause renal vasoconstriction, possibly by inhibiting release of NO and stimulation of renin.^{3,26}

RENAL DYSFUNCTION AFTER VASCULAR AND ENDOVASCULAR PROCEDURES

Renal dysfunction after vascular and endovascular procedures can vary from mild natriuresis to fulminant acute tubular necrosis (ATN) and acute renal failure (ARF). Postoperative renal

dysfunction can be classified as prerenal, renal, or postrenal (Fig. 46.2). The incidence of renal dysfunction complicating vascular and endovascular procedures has decreased with the development of appropriate fluid resuscitation, better surgical and endovascular techniques, and less nephrotoxic radiocontrast agents, although the mortality remains high (10% to 80%).^{27,28}

General Approach to Patients with Renal Dysfunction

Postoperative renal dysfunction is usually identified by oliguria or increases in serum creatinine.

Prerenal causes of renal dysfunction occur most frequently in the early postoperative period. A patient with signs of volume depletion requires replenishment of intravascular volume with physiologic saline (without potassium supplement until renal failure is ruled out). If diminished cardiac performance is responsible for the oliguria, judicious inotropic support is provided while indices of cardiac performance are measured.^{29,30} If correction of filling pressures or myocardial performance fails to improve urinary output, samples of urine and blood are obtained, and diuretic therapy is considered. Serum electrolytes, blood counts, and urine studies allow evaluation of other possible sources of oliguria such as ATN or myoglobinuria (Table 46.1).

Acute Renal Dysfunction: Causes

Prerenal causes are the most frequent source of acute renal dysfunction in the early postoperative period, most often

TABLE 46.1**Urinary and Blood Parameters in Renal Dysfunction**

Characteristic	Prerenal Dysfunction	Renal Parenchymal Dysfunction	Postrenal Dysfunction
Urine specific gravity	>1.020	1.010	1.012
Urine osmolarity (mOsm/L and mmol/kg)	>400	300 ± 20	300 ± 40
Urine/plasma osmolarity	>1.5	1	1
Urinary sodium (mEq/L)	<20	>30	<30*
Fractional excretion of sodium	<1%	>1%	<1%*
Urinary sodium/[urine/plasma creatinine]	<1	>1	<1
BUN/creatinine	20	10	10–20*
Urine/plasma creatinine	>40	<20	<20

BUN, blood urea nitrogen.

From Muther RS. Acute renal failure: acute azotemia in the critically ill. In: Civetta JM, Taylor RW, Kirby RR, editors. *Critical Care*, 2nd ed. Philadelphia, PA: JB Lippincott; 1992:1583–1598.

secondary to inadequate fluid replacement. Less commonly, it is secondary to a primary reduction in cardiac performance that triggers neurohormonal reflexes to enhance intravascular volume by increasing tubular reabsorption of sodium and water. Therapy for hypovolemic prerenal azotemia is to increase intravascular volume by administering balanced salt solution and red blood cells as needed, whereas renal dysfunction of cardiogenic origin is directed at improving myocardial performance by administering afterload-reducing and inotropic agents, and instituting diuretic therapy as needed.

In the vascular surgical patient population, identifying the cause of prerenal dysfunction (hypovolemic vs. cardiogenic) can be difficult. Preexisting heart disease may raise the baseline total body volume for an individual to higher central filling pressures, and apparently normal or low-normal cardiac filling pressures may reflect relative hypovolemia. In this clinical situation, one can maintain a constant infusion of afterload-reducing and inotropic agents (e.g., dobutamine) and cautiously administer small boluses of balanced salt solution. If no urinary response is noted when filling pressures begin to increase, diuretic therapy is added.^{31,32}

Another important prerenal cause of acute and chronic renal insufficiency is occlusive disease of the renal arteries: ischemic nephropathy. If other causes of prerenal dysfunction have been excluded, renal duplex sonography is used to determine whether occlusive disease of the main renal arteries is present (see Ch. 22, Vascular Laboratory: Arterial Duplex Scanning). When the duplex scan is positive,

contrast-enhanced angiography is performed to diagnose the problem prior to appropriate intervention.³³

Postrenal mechanisms represent the least frequent cause of postoperative oliguria. The obstructive process is usually at the level of the urethra or urinary catheter and less commonly at the level of the ureters. Hematuria or traumatic catheter insertion can predispose to clots and obstruction of indwelling urinary catheters. When rapid cessation of urine flow occurs, initial maneuvers should be directed toward catheter irrigation or replacement. Similarly, catheter kinking can occasionally cause obstruction. Postrenal oliguria can also be caused by ureteral or renal pelvic obstruction, and these mechanisms should be investigated after other causes of oliguria have been excluded. Causes include iatrogenic injury or compression of the ureters associated with aortic surgery, graft placement, and stone disease. A preliminary diagnosis can be suggested on the basis of renal ultrasound or isotope renography, and can be confirmed with retrograde urography. Therapy may require the placement of ureteral stents or percutaneous nephrostomy.²⁹

Clinical situations in which acute urinary retention can arise include voiding dysfunction after urinary catheter removal in patients with epidural catheters in place and in patients with prostatic hypertrophy. Generally, one should allow 6 to 12 hours to elapse after epidural analgesia is discontinued before removal of urinary catheters to avoid urinary retention. Prostatitis or traumatic urinary catheter insertion combined with general anesthesia can also precipitate acute urinary retention.

Parenchymal causes of acute renal dysfunction are diverse and pose the greatest risk for permanent renal failure. ATN describes all renal parenchymal causes of ARF. The pathophysiological mechanism of ATN involves a decrease in cellular ATP, which is associated with loss of the actin cytoskeleton; loss of the cytoskeleton causes a loss of renal tubular cell membrane polarity and subsequent loss of intercellular tight junctions. Shedding of the apical portion of tubular cells into the tubules can result in tubular obstruction and lead to a further reduction or cessation of glomerular filtration in the nephron. ARF is manifested clinically by an abrupt rise in serum creatinine, either with or without a change in urinary output (oliguria); it is sometimes possible to detect the presence of tubular cells in the urinary sediment on microscopic urinary evaluation. Although ATN may be transient, its causes related to vascular surgery include ischemic injury (shock, acute renal artery occlusion, multiorgan failure, and atheroembolic injury) and toxic injury (see the section below and Fig. 46.2).^{29,30}

ISCHEMIC INJURY TO THE KIDNEY

Acute Ischemic Renal Injury

Postoperative acute ischemic renal injury is caused by either temporary periods of interruption of renal perfusion or periods of systemic hypoperfusion. The pathophysiology of acute ischemic injury is twofold. First, as a consequence of the magnitude and duration of ischemia, tubular cell swelling occurs after reperfusion. This swelling can cause tubular obstruction, leading to a further reduction or cessation of glomerular

filtration in the nephron. Second, tubular cells either can lose their basement membrane attachment secondary to the interstitial edema that develops after reperfusion or can undergo cell death during ischemia, and subsequently be sloughed into the tubule. The medullary thick ascending loop of Henle and the pars recta of the proximal tubule seem to be the segments of the tubular epithelium that are most sensitive to ischemia. After loss of the tubular cell, back leak of glomerular filtrate into the renal parenchyma develops.^{30–36} The risk for acute renal dysfunction after a vascular surgical intervention is greatest for aortic surgery (see below).^{37–47}

Acute renal artery occlusion is discussed in Chapter 130 (Renovascular Disease: Acute Occlusive and Ischemic Events). When secondary to a cardioembolic event, the diagnosis is often delayed, and ultimate recovery of renal function depends on the magnitude of the occlusion and the presence of preexisting collaterals to the kidneys.⁴⁸ In renal artery dissection, functional recovery depends on the extent of the dissection, and the period of ischemia before surgical revascularization. Atheroembolism to the renal arteries has increasingly been recognized as a cause of ARF and can give rise to renal damage culminating in end-stage renal disease (ESRD). Up to 20% to 40% of patients with renal artery interventions have shown deterioration in GFR. It would seem logical to include use of distal embolic protection during these procedures. This is supported by the study of Henry et al.,⁴⁹ which showed that 100% of the patients treated with renal artery angioplasty and stents with distal filter wire protection showed evidence of emboli on the filter. Cooper et al.⁵⁰ showed that, in addition to distal embolic protection, adjunct pharmacologic treatment (such as the platelet glycoprotein IIB/IIIa inhibitor, abciximab) may be required to minimize renal injury after endoluminal interventions. Atherosclerotic plaque from proximal diseased aortic segments can complicate suprarenal cross clamping or manipulation of the aorta. Atheroembolism can also occur spontaneously from these proximal sources or from renal artery atherosclerotic plaque. The clinical diagnosis is suggested by deterioration of renal function in a patient who displays other extrarenal manifestations of atheroembolism (e.g., blue toe syndrome) and is highly suggested by the laboratory finding of eosinophilia (71%). The diagnosis is confirmed by renal biopsy, and treatment is supportive.^{51–54}

Vascular procedures complicated by sepsis, myocardial dysfunction, and reperfusion injury can result in transient or permanent renal dysfunction. In these instances, recovery of excretory renal function depends on elimination of the septic focus and improvement in left ventricular performance to ensure adequate renal perfusion.

Chronic Ischemia and Ischemic Nephropathy

Chronic ischemic nephropathy describes reduced renal excretory function in conjunction with renovascular disease. Usually, the renovascular disease is bilateral or involves a solitary kidney, and diminished renal artery perfusion. This condition tends to be rapidly progressive and is thought to be responsible for up to 20% of these patients becoming dependent on

dialysis. Uncorrected renovascular disease as a cause of ESRD is associated with a rapid rate of death during follow-up, with a median survival of only 27 months after the initiation of dialysis and a 5-year survival rate of just 12%. Patients who survive successful renal artery revascularization have an improved long-term survival (see Ch. 127, Renovascular Disease: Pathophysiology, Epidemiology, Clinical Presentation, and Medical Management).⁵⁵

In patients with recent worsening of renal function along with hypertension or taking an ACE inhibitor, the presence of ischemic nephropathy should be investigated. In contrast to renovascular hypertension secondary to unilateral renal artery stenosis, in which hypertension is renin dependent, hypertension in ischemic nephropathy tends to be volume dependent. Patients with this pattern of disease exhibit severe hypertension, elevated serum creatinine, and volume overload. Alternatively, the clinical manifestation may be recurrent episodes of flash pulmonary edema. This entity almost always coexists with some element of intrinsic renal disease.^{56–59}

Toxic Injury and Angiography

Aminoglycosides, myoglobin and radiologic contrast media are common nephrotoxic agents (Fig. 46.3). Aminoglycosides appear to exert their renal toxicity at the tubular cell by causing mitochondrial damage, destruction of the cell membrane, activation of phospholipase, or alteration in lysosomes. Risk factors include renal insufficiency, advanced age, extracellular volume depletion, and concomitant use of other nephrotoxins. The routine use of aminoglycoside blood levels to predict or prevent nephrotoxicity is probably not warranted. Alternative antibiotics with less nephrotoxicity have reduced the use of aminoglycosides in vascular surgical patients, all pharmacologic agents should be carefully chosen and the dosage adjusted for eGFR.^{30,60–62}

Myoglobinuria is an important cause of renal failure following revascularization after prolonged periods of limb ischemia. Myoglobin is filtered freely by the glomerulus, and exerts its toxicity through direct tubular cell injury and via precipitation and obstruction of the tubule. Hematuria after reperfusion of a profoundly ischemic extremity suggests pigment toxicity and should prompt urinalysis. Myoglobinuria is suggested when the urine is dipstick positive for blood but no red blood cells are present on microscopic analysis, and it can be confirmed by testing the urine for myoglobin. When diagnosed, renal injury may be lessened by maximizing the urine flow rate through the infusion of intravenous crystalloid and diuretics (mannitol) and by alkalinizing the urine (see Ch. 103, Acute Limb Ischemia: Evaluation, Decision Making, and Medical Treatment).⁶³

Contrast media-induced nephropathy (CMIN) now accounts for more than 10% of hospital-acquired renal failure with an associated increase in hospital mortality and cost.^{64–73} Ionic contrast agents have iodine incorporated into their structure to absorb X-ray photons, thereby achieving visualization of the vasculature. The principal site of CMIN is the renal tubule from transient regional ischemia.⁷⁴ Nonionic

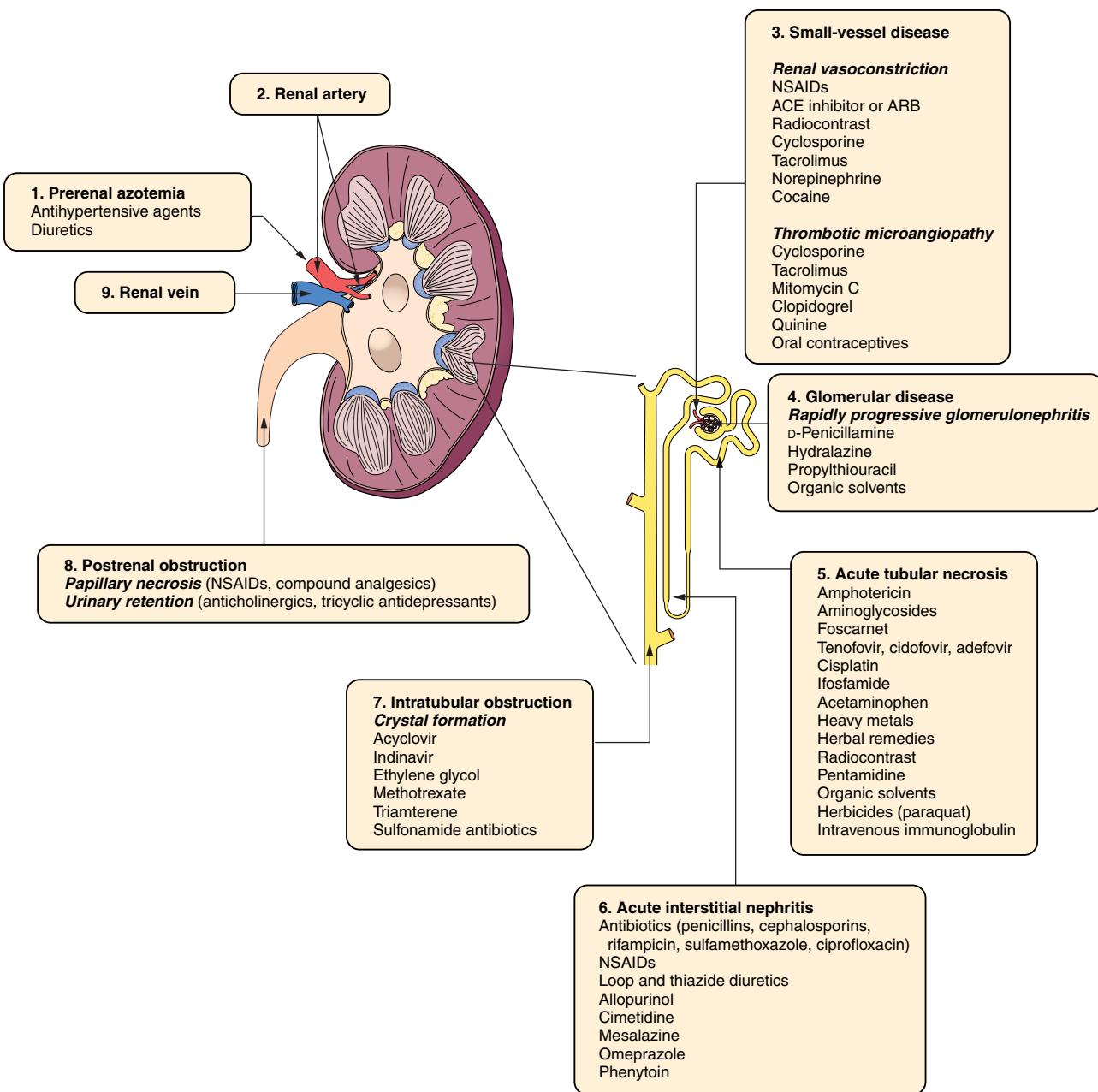


Figure 46.3 Nephrotoxic Agents That Lead to Acute Renal Failure. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs. (From Haseley L, Jefferson JA. Pathophysiology and etiology of acute kidney injury. In: Freehally J, et al. (eds). *Comprehensive Clinical Nephrology*, 6th ed. Philadelphia, PA: Saunders Elsevier; 2019:793.)

contrast agents provide comparable absorption of X-ray photons, yet are significantly less charged than traditional agents, although adverse renal events occur with the use of nonionic contrast media.⁷¹ CMIN occurs most commonly in patients with preexisting renal insufficiency (relative risk of 3.3) alone or in combination with diabetes mellitus, especially diabetes type 1. Other risk factors, such as dehydration, volume of contrast agent used, and simultaneous exposure to other nephrotoxins, contribute to the likelihood of CMIN.⁷⁰ Additional risk factors include multiple myeloma and heavy proteinuria. The incidence of CMIN after contrast-enhanced angiography

varies from 0% to 12%. In patients with normal renal function, the incidence of (CMIN) is just 1% to 2%.⁷¹ Although diabetic and nondiabetic patients with renal insufficiency are at increased risk for CMIN, diabetics recover less often and are at greater risk for permanent dialysis.⁷⁴⁻⁷⁹

The biochemical mechanisms of CMIN have not been identified. One group of studies has hypothesized that NO and vasodilator prostaglandins (PGE2) contribute to preservation of renal blood flow and function in normal and pathologic states. Several studies have shown that inhibition of NO, before the administration of radiocontrast material, results in abolition of

the medullary vasodilatory response and contributes to regional hypoxic renal tubular injury.^{80–83} Myers et al.⁸⁴ combined the use of *in vivo* microdialysis and laser Doppler blood flow analysis to suggest that the down-regulation of renal cortical and medullary NO synthesis contributed to the contrast-induced loss of renal cortical and medullary microvascular blood flow.⁸⁴

The risk for CMIN seems to be related to the amount of time that the kidney is exposed to the contrast material. Therefore, maximizing the urine flow rate during and immediately after angiography and limiting the quantity of contrast agent used are beneficial. Maximal urine flow rates should be achieved by preliminary intravenous hydration of the patient. Hydration with 0.45% saline provides better protection against CMIN rather than hydration with 0.45% saline plus mannitol or furosemide.⁸⁵ One regimen treats any patient with the aforementioned risk factors 12 hours before angiography with intravenous hydration at 1.5 mL/kg per hour. Immediately before angiography, the patient usually receives a bolus of intravenous fluid (3 to 5 mL/kg). Finally, intravenous hydration is continued for 4 to 6 hours after completion of the study. Merten et al.⁸⁶ demonstrated the potential efficacy of sodium bicarbonate hydration before, during, and after the use of contrast agents. In this regimen, patients are treated with 154 mEq/L of sodium bicarbonate with a bolus of 3 mL/kg, followed by 2 mL/kg per hour for 6 hours after the procedure. Figure 46.4 provides an approach to management of patients receiving iodinated contrast.⁸⁷

No definite safe upper limit of contrast material currently exists. Even small doses (30–60 mL) may induce renal failure in

patients with extreme renal insufficiency (GFR \leq 15 mL/min). Conversely, more than 300 mL of contrast material may be administered safely to other patients with no risk factors for ARF.⁸⁸ However it seems prudent to limit the quantity of nonionized contrast agent to less than 50 to 75 mL in patients with a significant reduction in GFR (<20 to 30 mL/min). In addition to the use of digital subtraction techniques, carbon dioxide gas can be used for angiography with minimal renal risk.⁸⁹ Another alternative is the use of abdominal ultrasound with visceral and/or renal artery duplex sonography. Use of magnetic resonance angiography with gadolinium-based contrast agents is no longer considered a viable option in these cases because of reports of nephrogenic fibrosis in patients with compromised renal function.⁹⁰

N-acetylcysteine (scavenger of reactive oxygen species) may protect against CMIN. Tepel et al.⁹¹ documented a significant reduction in serum creatinine with the use of oral N-acetylcysteine and hydration versus placebo and hydration in patients with chronic renal insufficiency.⁹¹ However, there are as many studies showing either a benefit or no benefit from the use of acetylcysteine.^{92–94} Finally, high-dose loop diuretics, ACE inhibitors, and angiotensin II receptor antagonists are withheld for at least 72 hours before aortic surgery or exposure to arterial contrast. Selective beta blockers and calcium channel blockers are substituted when necessary.

Several recent reviews have examined CMIN in patients undergoing peripheral and endovascular interventions. In an analysis of the Vascular Quality Initiative database from 2010 to 2018, increasing stage of CK was associated with increased

Management of Patients Receiving Iodinated Contrast Media

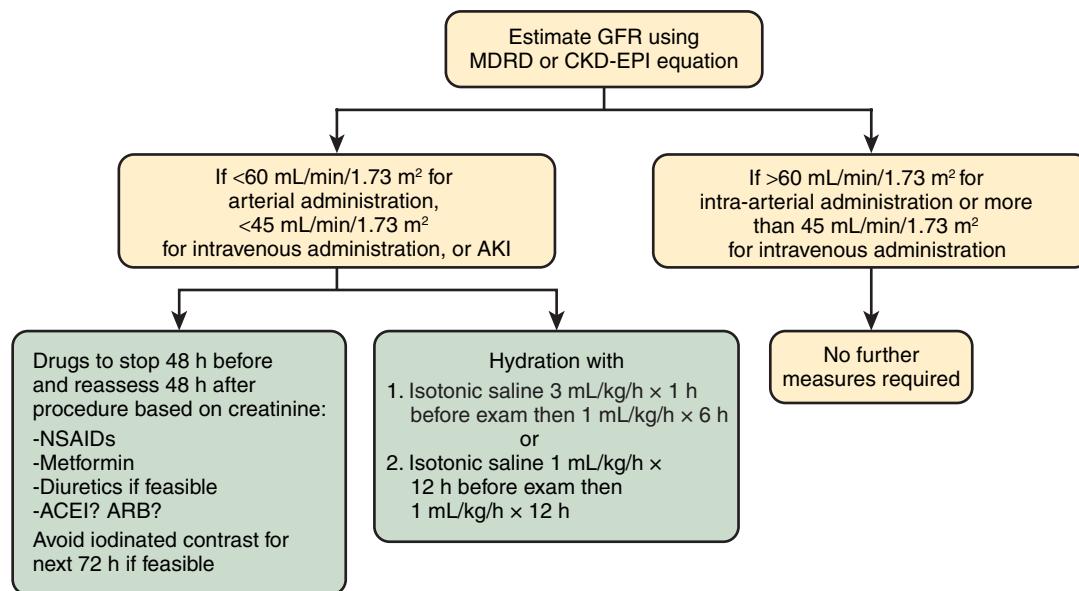


Figure 46.4 Management of Patients Receiving Iodinated Contrast Media. ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NSAIDs, nonsteroidal anti-inflammatory drugs. (From Bouchard J, et al. Prevention and nondialytic management of acute kidney injury. In: Freehally J, et al., eds. *Comprehensive Clinical Nephrology*, 6th ed. Philadelphia, PA: Saunders Elsevier; 2019:828.)

incidence of CMIN. They also showed the safe thresholds for contrast volume for advanced CKD were 50, 20 and 9 mL for CK3, CK4 and CK5, respectively.⁹⁵ In another report, pre-existing CKD, intra-arterial administration and CM volume were identified as the most important risk factors for CMIN.⁹⁶ This study suggested that more data is needed on aggressive volume expansion strategies and targeted forced diuresis with high urinary output as protective strategies. The role of anti-oxidant agents remains controversial, but there is moderate evidence supporting N-acetylcysteine. Statins could reduce the incidence of CMIN although the mechanism of action is not known. Peri-procedural hemodialysis/hemofiltration seem aggressive and carry unnecessary risks. Remote ischemic preconditioning might represent a simple, noninvasive and cost-effective preventive measure for CMIN but few data are available about its clinical application in patients at high risk for CMIN.⁹⁶ In a meta-analysis including eight studies (7 observational and 1 randomized control study) and 677 patients who underwent 754 angiographic procedures, carbon dioxide was associated with a decreased incidence of CMIN (4.4% vs. 11.1%). A subgroup analysis of four studies showed carbon dioxide given patients with CKD (stage not identified) had a decreased rate of CMIN versus contrast medium but it was not statistically significant. Interestingly, carbon dioxide was associated with increased risk of other non-renal events including limb/abdominal pain and nausea and vomiting.⁹⁷

ALTERED RENAL FUNCTION DURING AORTIC SURGERY

Fluid Shifts Associated with Aortic Surgery

Abdominal aortic surgery is associated with volume shifts within fluid compartments secondary to local tissue trauma from operative dissection, hemodynamic consequences of aortic clamping and unclamping, and from operative blood loss. The changes are largely mediated through transcapillary and transcellular movement of fluid. The net movement of water and solutes from the intravascular, extracellular compartment (plasma) to the interstitium (extracellular or third space) normally takes place at the precapillary level secondary to increased hydrostatic pressure. Reentry of fluid back into the intravascular compartment in the distal capillaries is favored by the presence of the intravascular protein albumin, which exerts an oncotic pressure gradient. Normally, 7% of the intravascular albumin arriving at the capillary level crosses the capillary membrane into the interstitial space. This extravascular protein eventually enters the lymphatics and ultimately returns to the intravascular pool. The operative dissection that occurs during aortic surgery results in disruption of lymphatic channels and the release of inflammatory mediators that cause local and systemic alterations in tissue perfusion, thereby contributing to an increase in the permeability of capillary membranes to albumin.⁹⁸ The resultant effects are a flux of albumin into the interstitium and subsequent decrease in water reabsorption into the intravascular space which activates neuroendocrine mechanisms that decrease renal excretion of sodium and free water. In addition,

there is net movement of sodium and water into the intracellular space from the extracellular compartment. This is due to a relative decline in the normal cellular transmembrane potential after ischemia-reperfusion, shock, or both, secondary to blood loss.⁹⁹ The causes of the decline in transmembrane potential are unclear, but are due, in part, to impaired function of the Na⁺, K⁺-adenosine triphosphatase, loss of active ion transport and an increase in the intracellular level of calcium.⁹⁹ Resuscitation reverses these changes in ion transport and cellular edema. The normal response to decreased circulating intravascular volume is to mobilize extracellular (third-space) interstitial fluid. The presence of temporary ischemia shift in acid-base balance in tissue beds during aortic surgery, the adverse impact of unreplaced blood loss, the potential reductions in cardiac and renal performance during aortic cross clamping, and stimulation of stress-induced neuroendocrine mechanisms contribute to the injury-induced shift of total body water from the functional circulating blood volume into the third space.^{100,101}

Determination of intravascular volume and its associated solutes after major surgery has been of dramatic benefit to the intraoperative and early postoperative fluid management of vascular surgery patients. The increased obligatory losses of intravascular volume associated with major surgery have led to the current use of balanced salt solutions (5% dextrose, lactated Ringer solution) for volume replenishment.¹⁰² Hourly postoperative fluid requirements may be several-fold higher than requirements during the resting state. The increased need for fluid replacement continues in the immediate postoperative period because of continued sequestration of fluid into areas of the operative site and the persistent effects of inflammatory mediators.¹⁰³ Mobilization of the sequestered third-space fluid is delayed for 2 to 5 days, depending on the magnitude of operative and postoperative stress, cardiac performance, and intravascular oncotic pressure. Reabsorption of third-space fluid usually begins on postoperative day 2 or 3. If not managed with an appropriate reduction in maintenance parenteral fluids or diuretic therapy, reabsorption of third-space fluid can lead to intravascular volume overload and acute congestive heart failure.

Although renal insufficiency continues to be a complication after treatment of suprarenal aneurysms and renal artery occlusive disease, very few studies have assessed the effect on renal function of clamping the aorta above and below the renal arteries. A series of studies by Myers et al.^{104–106} examined whether suprarenal aortic clamping and reperfusion above the renal arteries (renal-SRACR) preserves renal function as opposed to clamping the renal arteries above the superior mesenteric artery (SMA-SRACR). In an experimental model, both SMA-SRACR and renal-SRACR were shown to decrease medullary and cortical blood flow and NO synthesis. SMA-SRACR downregulated cortical iNOS, whereas renal-SRACR did not. The cortex and medulla responded to the decreased blood flow and NO synthesis by increasing PGE2 synthesis after renal-SRACR, which was due to increased COX-2 content. The use of superoxide dismutase (inhibitor of oxygen-derived free radical [ODFR] formation), restored cortical and medullary NO synthesis after SMA-SRACR (but not

renal-SRACR), suggesting that the ODFRs generated during mesenteric ischemia-reperfusion were one of the systemic mechanisms contributing to decreased renal NO synthesis. SMA-SRACR profoundly decreased creatinine clearance, far greater than the decrease in clearance that occurred after renal-SRACR. These data suggest that cortical and medullary vasodilators (NO and vasodilator prostanoids) are required to maintain microvascular renal cortical and medullary blood flow after both SMA-SRACR and renal-SRACR. The data also suggest preventing or inhibiting ODFR production during SMA-SRACR could help maintain renal microvascular blood flow.^{104–106}

Renal Failure Associated with Aortic Surgery

Aortic repair requiring suprarenal cross clamping poses a significant risk for an ischemic renal insult, and the risk is greater for repair of thoracoabdominal aneurysms, in which longer periods of renal ischemia can be anticipated. Rates of ARF approaching 18% have routinely been quoted for elective repair of thoracoabdominal aneurysms in larger series. Recovery of renal function after suprarenal aortic cross clamping depends on preexisting renal dysfunction, patient age, and duration of renal ischemia. Periods of hypotension as a result of blood loss, myocardial dysfunction, or sepsis can also diminish renal blood flow and induce ARF.^{37–40} The occurrence of renal failure after repair of infrarenal aortic aneurysms and aortic surgery ranges from 1% to 13%.^{34–47} Mortality in patients with postoperative renal failure as an isolated system failure ranges from 25% for nonoliguric renal failure to 70% for oliguric renal failure.^{37–47,107–109} When renal failure is only one of several system failures, mortality is extremely high, approaching 100%.^{30,107–113} Unfortunately, the pathophysiology, and thus, the prevention of multiorgan system failure have not been elucidated.

A temporary isolated period of renal ischemia caused by suprarenal aortic cross clamping, temporary renal artery occlusion, a single episode of hypovolemic shock, post-cross clamp hypotension, or cardiogenic shock in the perioperative period are the most common causes of acute renal dysfunction associated with aortic surgery. Several important studies have postulated that a pathophysiologic cascade of events leads to ARF after temporary renal ischemia.^{114–120} Renal biopsy specimens and autopsy studies in patients with postischemic ARF have shown minimal disturbance in glomerular architecture, yet profound disruption of tubular morphology.

Clinically observed rates of renal failure after aortic surgery suggest that the incidence of ARF can be correlated with the level of aortic repair. Svensson et al.,¹⁰⁸ Kashyap et al.,¹⁰⁹ and Allen et al.¹¹⁰ reported an 18% incidence of renal failure (serum creatinine >3 mg/dL [$>265 \mu\text{mol/L}$]) and a 9% rate of dialysis-dependent renal failure in patients who underwent thoracoabdominal aneurysm repair. Series using regional renal hypothermia for renal protection and a clamp-and-sew technique identified the occurrence of ARF in 11.5% of patients.^{108–110} Factors that predicted renal dysfunction included a preoperative creatinine level greater than 1.5 mg/dL

(133 $\mu\text{mol/L}$) and a total cross-clamp time of more than 100 minutes. These results do not seem to differ from series in which partial left heart bypass and distal aortic perfusion were used.¹⁰⁸ In cases of juxtarenal and suprarenal abdominal aortic aneurysm (AAA) repair, preservation of renal function may be enhanced by renal hypothermia.¹⁰⁹ For elective infrarenal aortic surgery, a preoperative creatinine clearance of less than 45 mL/min has been associated with a significant risk for subsequent renal failure. In the same series, no patient with a preoperative serum creatinine concentration of less than 1.5 mg/dL (133 $\mu\text{mol/L}$) required postoperative dialysis as opposed to 8% with a preoperative creatinine level greater than 1.8 mg/dL.¹⁰⁹

Another important cause of ARF in aortic surgery is renal atheroembolism.^{121,122} In the absence of other factors favoring ARF and a normal mass of functioning nephron units, relatively large amounts of atheromatous microemboli can accumulate without an immediate impact on renal function.¹²² In contrast, in patients with minimal renal reserve, even minor microembolization can lead to ARF.

The use of endovascular aneurysm repair (EVAR) has also been associated with an increased risk of renal dysfunction. This can be secondary to direct trauma to the renal arteries with suprarenal fixation barbs or dissection of the renal artery during reposition of a maldeployed aortic endograft with suprarenal barbs.^{123–127} Interestingly, renal dysfunction has been observed during long-term follow-up after EVAR. The causes for this are unknown at this time. In an analysis of the VQI from 2003 to 2014 including 14,475 patients, following EVAR it was noted that 2.9% developed acute kidney injury and 0.4% developed a new hemodialysis requirement. Five-year survival was 77.5% in the group without acute renal injury, 53.5% in the group with acute renal injury and the 3-year survival was 22.8% in the group requiring hemodialysis. The factors that correlated with acute kidney injury were new-onset congestive heart failure and return to the operating room with vasopressor requirement, whereas a GFR greater than 60 mL/min per 1.73 m^2 was protective. Interestingly no correlation was found between contrast volume and postoperative renal dysfunction.^{128,129} Another analysis of the VQI database was performed to identify predictors of acute kidney injury in octogenarians undergoing both open (OAR) and endovascular (EVAR) AAA repair. From 2003 to 2017, 27,993 patients (12% OAR and 88% EVAR) were included, of which 6708 (24%) were octogenarians (OAR, 332; EVAR, 6376). Postoperative AKI was more common in octogenarians in OAR (15.1% vs. 10.1%) and EVAR (4.2% vs. 2.7%). Thirty day mortality after AKI was higher in octogenarians whether undergoing OAR (28.0% vs. 8.8%) or EVAR (14.1% vs. 7.5%).¹³⁰ Independent risk factors included OAR, COPD, chronic kidney disease stage III–V, peripheral vascular disease, aneurysm diameter, and preoperative beta blocker use (Fig. 46.5).

In a study of complications following open and endovascular (using branched or fenestrated endografts) for TAAA repair, endovascular repair was associated with lower rates of postoperative dialysis 6.4% vs 12.0% but similar rates of being

Chronic Kidney Disease Classification According to Glomerular Filtration Rate and Albuminuria

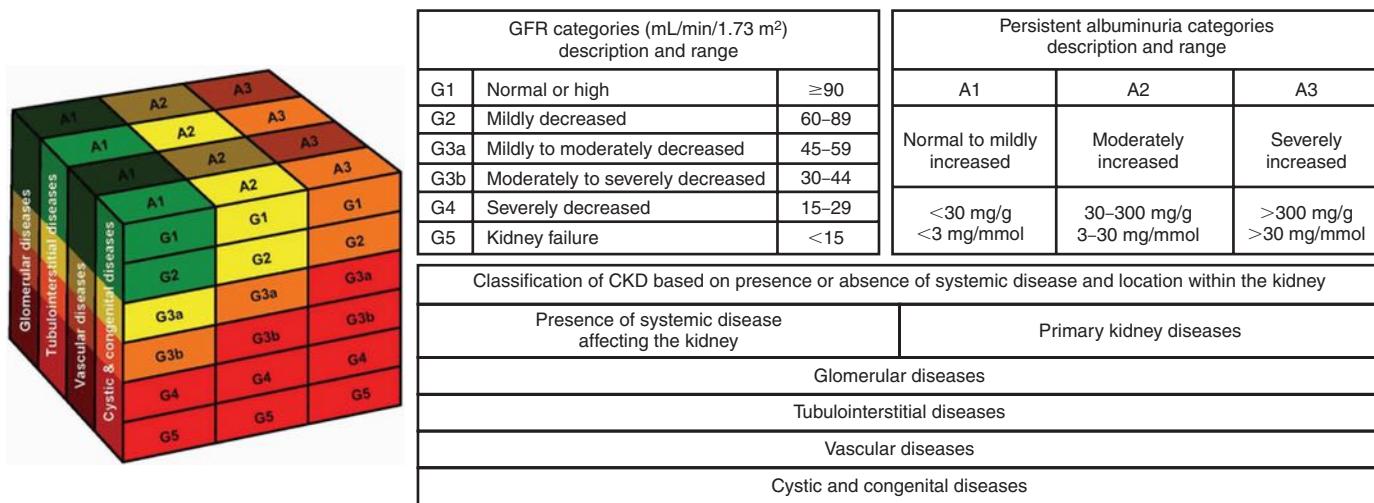


Figure 46.5 Depiction of Chronic Kidney Disease Classification, G-Stages and A-Stages. The cube denotes how the three components of the chronic kidney disease classification scheme (glomerular filtration rate [G], albuminuria [A] and underlying kidney disease) interact to influence the risk of progression to kidney failure. This risk is represented in qualitative terms (lowest to highest) by green, yellow, orange and red colors. (From Grams ME, McDonald SP. Epidemiology of chronic kidney disease and dialysis. In: Freehally J, et al., eds. *Comprehensive Clinical Nephrology*, 6th ed.. Philadelphia, PA: Elsevier Saunders; 2019:904.)

discharged on permanent dialysis.¹³⁰ De Souza et al. compared renal outcomes in patients treated with EVAR (134) or with TAAA patients treated with fenestrated endovascular repair FEVAR (67). A greater than 25% decrease in eGFR was seen in 5% of FEVAR and 9% of EVAR patients at 1 month. There was a progressive decrease in eGFR in both groups at 2 years and 5 years but they were not statistically different. Progression to stage IV–V CKD was similar at 2 years (FEVAR 2%; EVAR 3%) and 5 years (FEVAR 7%; EVAR 9%). There was statistically more renal artery stenosis/occlusions (FEVAR 22%, EVAR 2%) and renal-related re-interventions (FEVAR 18%, EVAR 3%). Progression to renal failure requiring dialysis was low in both groups (1.5%).^{131,132} Wang et al. examined 120 FEVAR patients to determine the impact of AKI on long-term renal function. Twenty-four patients (20%) exhibited postoperative AKI. Four patients required perioperative dialysis, 3 of which resolved before discharge. AKI patients demonstrated a 57.1% increase in serum creatinine at 1 month following surgery which decreased to 14.3% at 6 months.¹³³ Unlike Rocha's study, Wang et al. did not see an elevation in serum creatinine at 2 years follow-up (see Ch. 79, Thoracic and Thoracoabdominal Aneurysms: Open Surgical Treatment; Ch. 81, Thoracoabdominal and Aortic Arch Aneurysms: Strategies for Operative Repair; and Ch. 82, Fenestrated and Branched Endograft Treatment of Juxtarenal, Paravisceral, Thoracoabdominal, and Aortic Arch Aneurysms).^{131,133} These studies show that complex suprarenal aneurysms, treated in high volume very experienced institutions, can be performed with a relatively low risk of AKI or CKD.

Protection of Renal Function During Aortic Surgery

Strategies to protect renal function during aortic surgery include limiting the period of warm renal ischemia, providing intravenous fluid hydration preoperatively, adequately replacing blood volume during and immediately after surgery, avoiding repetitive or prolonged renal ischemia, and maintaining maximal parameters of cardiac performance. Other protective measures include the use of mannitol, furosemide, and other diuretics; renal hypothermia; and renal vasodilating drugs.^{127–144} While no single modality or combination of modalities entirely prevents renal injury during aortic surgery, one can lessen the severity and duration of renal dysfunction. For a normally perfused kidney, less than 40 minutes of warm ischemia is well tolerated. For a chronically ischemic kidney, the duration of safe warm ischemic time is decreased but variable, depending on the amount of collateral flow. Preoperative evaluation and intraoperative preparation can help reduce the ischemic time and diminish complications.^{127–144}

Other measures that lessen the risk for ARF include routine heparinization (with confirmation of systemic anticoagulation by measurement of the activated clotting time) and the intravenous administration of mannitol before aortic cross clamping. Mannitol not only acts as an osmotic diuretic to increase the urine flow rate but may also attenuate the reduction in cortical blood flow that occurs during and immediately after aortic cross clamping. In addition, mannitol acts as a scavenger of oxygen-derived free radicals and appears to decrease subclinical glomerular and renal tubular damage. However, some data are conflicting

regarding the benefit of mannitol.^{127,142–145} Patients with CKD are at highest risk for AKI when surgical occlusion of the aorta is prolonged. AKI after aortic surgery requires aggressive therapy, and the goal should be correction of extracellular volume deficits. Conversion of oliguric to a nonoliguric renal failure is associated with decreased morbidity and mortality.^{127–142}

Low-dose dopamine in healthy adults causes increases in renal perfusion, GFR, and urine output.^{145–147} However, the clinical benefit of prophylactic dopamine administration in patients undergoing aortic surgery is unproved. Because dopamine may cause tachyarrhythmias, myocardial ischemia, pulmonary shunting, or mesenteric vasoconstriction, its routine use should be approached with caution.^{145–153}

Fenoldopam is a dopaminergic type 1 (DA1) receptor agonist that may reduce the risk for ARF. Two dopamine receptors are found in the kidney: DA1 and DA2. Activation of the DA1 receptor causes an increase in GFR, probably mediated by increased blood flow to the inner cortex and medulla of the kidney. Activation of the DA2 receptor causes a reduction in renal blood flow and GFR.^{154–157} Because it is a selective DA1 agonist, fenoldopam significantly increases renal blood flow in healthy adults and in animal models of CMIN.¹⁵⁸

Atrial natriuretic peptide is an endogenous hormone released from the cardiac atria that has vasodilatory, diuretic, and natriuretic properties. Atrial natriuretic peptide and fenoldopam infusions have shown benefit in preventing CMIN and renal dysfunction after cardiac surgery. Their role in patients undergoing aortic surgery is not yet defined.^{159–162}

Distal aortic perfusion may be used to maintain renal perfusion during repair of thoracoabdominal aneurysms. This technique is most attractive during the repair of an isolated thoracoabdominal aneurysm¹⁵⁰ or when complex disease precludes prompt completion of the proximal thoracic aortic anastomosis.¹⁵¹ Distal aortic perfusion may be modified with “octopus” catheters to perfuse the renal arteries directly during distal reconstruction.¹⁵² Because the routine use of distal aortic perfusion has been associated with an increased incidence of AKI despite spinal cord protection in patients with extensive (type II) thoracoabdominal aneurysm, other strategies to provide renal protection may be considered.¹⁵³

Regional renal hypothermia has been used sporadically for many years to protect renal function during periods of ischemia. The technique usually involves the infusion of 500 mL to 1 L of cold (4°C–5°C) crystalloid solution, with or without other additives, into the isolated segment of the aorta containing the renal arteries or directly into the renal artery ostia via a hand-held cannula or infusion balloon catheter. The protective effect of minimal changes in core temperature has been evaluated in rats. The first 10°C reduction in tissue temperature seems to provide the greatest protection. Postoperative serum creatinine levels and renal tubular morphology data revealed that a protective effect occurs with a minimal sustained decrease in core temperature to 35°C.^{163–170}

Operative technique during aortic reconstruction should avoid repetitive aortic cross clamping to minimize the risk for microembolization to the kidney and other of distal vascular beds. Some authors use temporary renal artery occlusion immediately

before application of the aortic cross clamp whenever there is the presence of complicated perirenal artery atherosclerosis.

Occasionally the surgeon may facilitate the exposure of the suprarenal aorta and expedite repair by transecting the left renal vein (LRVD). Because of the collateral drainage of the left kidney, it is thought that permanent ligation of the LRV may be a safe procedure, without reconstruction. It is not common practice to reconstruct the vein following LRVD, yet no clear guidelines exist. Marrocco-Trischitta et al.¹⁷¹ showed that LRVD did not show significant differences in postoperative GFR trend, operative time, blood loss, perioperative complications, hospital stay, and renal function tests obtained at 6 months after surgery. Samsonn et al.¹⁷² treated 56 patients with LRVD (9 for aorto-iliac disease and 47 for AAAs). All but two patients had stable renal function after the LRVD. Two patients had serum creatinine that increased to 2.1 and 2.4 mg/dL but remained stable long-term. Several series have shown increased renal dysfunction following LRVD. In a large series, West et al.¹⁷³ reported increased pulmonary and renal complications following LRVD in patients with pararenal aortic aneurysms. Mehta et al.¹⁷⁴ showed that patients treated with LRVD had decreased renal function on day 1 compared with baseline. However, the decrease in renal function returned to baseline levels by day 7 and 2 to 6 weeks after surgery. The main tributaries are the left gonadal vein, the left ureteral vein, capsular veins, lumbar veins and the ascending lumbar vein, the left middle suprarenal vein and the inferior phrenic vein from below so LRVD toward the inferior vena cava will spare the tributaries and thus preserve renal function.

MEDICAL MANAGEMENT OF ACUTE RENAL FAILURE

ARF is characterized by a rapid decline (days to weeks) in GFR, such that it is not sufficient to decrease uremic toxins. Urine volume in ARF is variable and determined by both the GFR and tubular reabsorption. Renal injury causes are typically tubular and vascular factors (see Fig. 46.2).³⁰ Two classification systems have been developed to replace the RIFLE criteria: KIDGO and AKIN (Table 46.2). Increasing severity of AKI based creatinine and reduction in urine output is associated with increased risk of death.^{30,62} The first approach to patients with ARF involves the treatment of fluid and electrolyte disturbances, as well as the metabolic state (Table 46.3).

Many patients with CKD will progress to ESRD. At a GFR less than 60 mL/min, one must begin prophylaxis against secondary hyperparathyroidism by restricting dietary phosphate and the use of phosphate binders. Deficiency of 25-hydroxyvitamin D3 is treated, by 1α-hydroxyvitamin D₃ or 1,25-dihydroxyvitamin D. Iron status and anemia should be treated if necessary, and immunization against hepatitis B virus instituted. At a GFR of less than 15 to 20 mL/min, the alternatives of dialysis and early renal transplantation should be discussed.^{30,174} A step wise approach to the evaluation with a patient who develops acute azotemia in the postoperative period is presented in the chapter algorithm.¹⁷⁵

TABLE 46.2

Classification of Chronic Kidney Disease Based on the Glomerular Filtration Rate as Proposed by the Kidney Disease Outcomes Quality Initiative Guidelines

CKD Stage	Description
1	Normal or increased GFR; some evidence of kidney damage reflected by microalbuminuria/proteinuria, hematuria, or histologic changes
2	Mild decrease in GFR (89–60 mL/min/1.73 m ²)
3	Moderate decrease in GFR (59–30 mL/min/1.73 m ²)
4	Severe decrease in GFR (29–15 mL/min/1.73 m ²)
5	GFR <15 mL/min/1.73 m ² ; when renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life

CKD, chronic kidney disease; GFR, glomerular filtration rate.

Adapted from EL Kassi M, et al. Epidemiology and pathophysiology of chronic kidney disease, natural history, risk factors, and management. In: Freehally J, Floege J, Johnson R (eds). *Comprehensive Clinical Nephrology*, 3rd ed. Philadelphia, PA: Mosby Elsevier; 2007:813.

DIALYSIS

In 2017, 746,557 Americans needed dialysis or kidney transplantation. The annual mortality rate internationally still remains 15% to 25%. The aim of hemodialysis (HD) is to deliver the patient's blood in a safe manner to the dialyzer and enable efficient removal of uremic toxins. The treatment index, Kt/V, is the most widely used parameter for assessment of the dialysis dose. Factors influencing Kt/V include blood and dialysate flow rate, efficiency of the dialyzer, effective surface area of the dialyzer, hematocrit, anticoagulation, and recirculation. The time, t, is also important for reaching the Kt/V target. A Kt/V of 1.2 indicates removal of 63% of total body urea. If one doubles the Kt/V to 2, there is only an additional 24% increase in removed urea. The current recommendation is to achieve a Kt/V of 1.3, which can be assessed on a monthly basis. A maximum Kt/V of 3.0 can be achieved with efficient dialysis performed three times per week.¹⁷⁴

Ultrafiltration and Hemofiltration

Ultrafiltration and hemofiltration are techniques that remove large volumes of fluid with minimal removal of metabolic wastes. These filtration techniques are useful for removing fluid from patients with acute renal insufficiency in the intensive care setting after major vascular reconstructions. Ultrafiltration is similar to HD, except that no dialysate is used. Arterial blood is applied across a dialyzer membrane under negative pressure, which causes an ultrafiltrate of plasma to form and be removed.¹⁷⁴ Hemofiltration techniques include slow continuous venovenous hemofiltration (CVVH) alone or with hemodiafiltration (CV-VHDF) and continuous arteriovenous hemofiltration (CAVH) alone or with hemodiafiltration (CAVHDF). In CAVH and CAVHDF, blood flows from an arterial catheter into a dialyzer and is returned to the patient through a venous catheter.¹⁷⁴

TABLE 46.3

Supportive Management of Acute Renal Failure

Complication	Treatment
Intravascular volume excess	Restrict salt (1–2 g/day) and water (usually <1 L/day) intake Administer diuretics (usually loop diuretics fl thiazides) Perform ultrafiltration or dialysis
Hyponatremia	Restrict free water intake (<1 L/day) Avoid hypotonic intravenous solutions (including dextrose solutions)
Hyperkalemia	Restrict dietary K ⁺ intake (usually <30 mmol/day) Eliminate K ⁺ supplements and K ⁺ -sparing diuretics Administer potassium-binding ion exchange resins Administer glucose (50 mL of 50% dextrose) and insulin (10 units) Administer sodium bicarbonate (usually 50–100 mmol) Administer β ₂ -agonist inhaled (e.g., albuterol [salbutamol], 10–20 mg inhaled or 0.5–1 mg IV) Administer calcium gluconate (10 mL of 10% solution over period of 2–5 minutes)
Metabolic acidosis	Restrict dietary protein (usually 0.8–1.0 g/kg/day of high biologic value) Administer sodium bicarbonate (maintain serum bicarbonate >15 mmol/L and arterial pH >7.2)
Hyperphosphatemia	Restrict dietary phosphate intake (usually <800 mg/day) Administer phosphate-binding agents (calcium acetate, calcium carbonate, aluminum hydroxide, and sevelamer)
Hypocalcemia	If symptomatic: administer IV calcium gluconate (10–20 mL of 10% solution) or IV calcium chloride (10–20 mL of 10% solution via central line) If asymptomatic: administer calcium carbonate, 500 mg orally three times daily
Hypermagnesemia	Discontinue magnesium-containing antacids
Hyperuricemia	Treatment usually not necessary if uric acid <15 mg/dL (<900 μmol/L)
Nutrition	Restrict dietary protein (0.8–1.0 g/kg/day) if not catabolic Administer carbohydrate (>100 g/day, adjust according to nonprotein calorie requirement) Provide enteral or parenteral nutrition (if prolonged course or very catabolic)

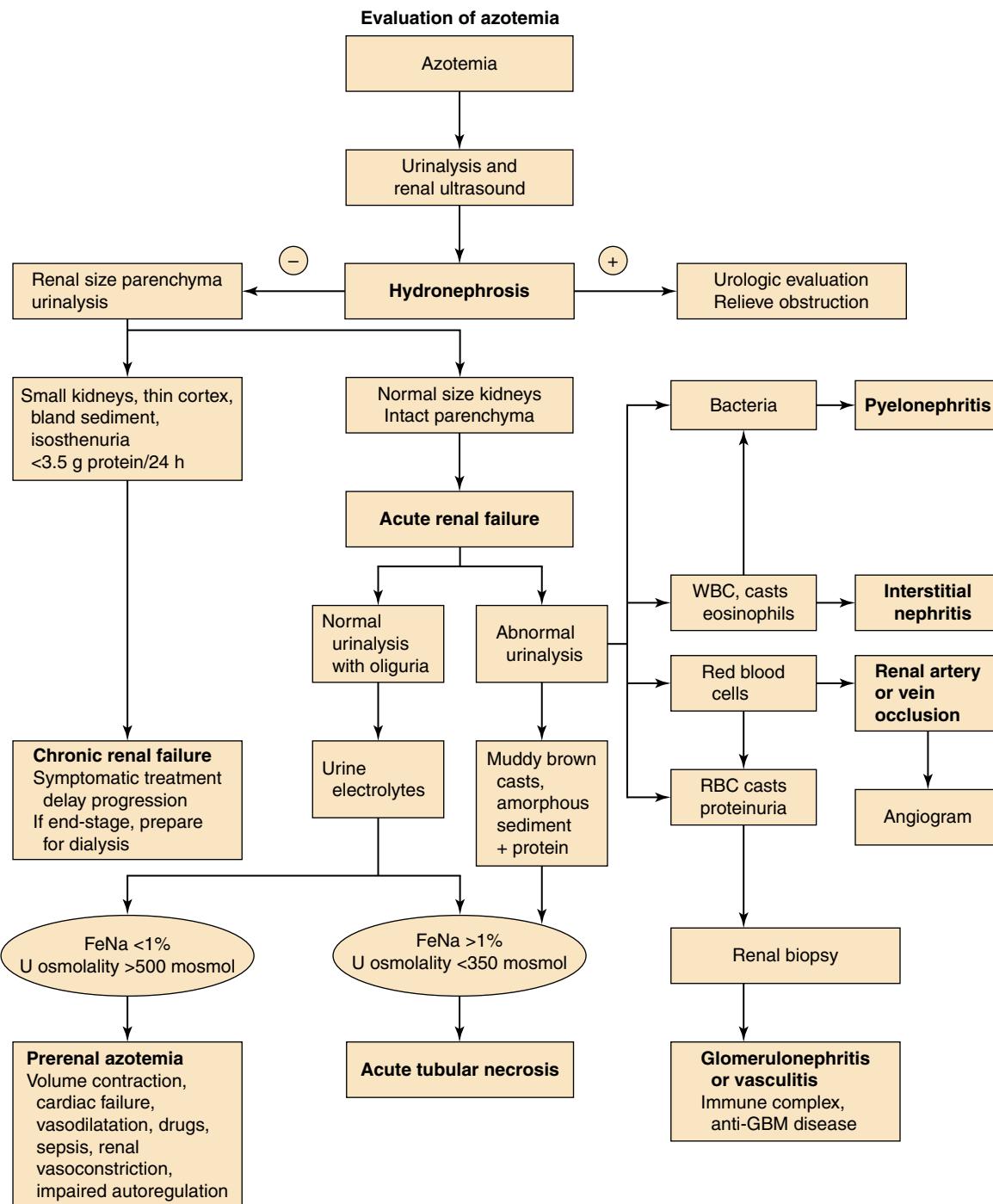
Adapted from Ejaz AA, et al. Nondialytic management of acute renal failure in Freehally J, Johnson R, Floege J, eds. *Comprehensive Clinical Nephrology*, 3rd ed. Philadelphia, PA: Mosby Elsevier; 2007:787.

Peritoneal Dialysis

Peritoneal dialysis (PD) can be used instead of HD. Between 8% and 9% of the total dialysis population is treated with PD (approximately 120,000 patients). With this technique, the peritoneal cavity becomes the dialysis membrane and is used to hold between 2 and 2.5 L of sterile dialysis

fluid. PD is best used in patients who have some residual renal function. Advantages include slow exchange of solutes and excess body water, and avoidance of the need for vascular access. Contraindications include large diaphragmatic defects, peritoneal adhesions, surgically uncorrectable hernias, acute ischemic bowel, or intraperitoneal infectious processes.^{174,176}

CHAPTER ALGORITHM



Approach to the Patient with Azotemia. *FeNa*, fractional excretion of sodium; *GBM*, glomerular basement membrane; *RBC*, red blood cell; *WBC*, white blood cell.

(Adapted from Mount DB. Azotemia and urinary abnormalities. In: Jameson J., et al., eds. *Harrison's Principles of Internal Medicine*, 20th ed. New York: McGraw-Hill; 2018.)

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A complete reference list can be found online at www.expertconsult.com.

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Systemic Complications: Neurologic

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INTRODUCTION 602

ISCHEMIC NEUROPATHY 602

Acute Ischemic Neuropathy 603

Chronic Ischemic Neuropathy 603

TRAUMATIC NERVE INJURIES 603

OTHER CAUSES OF NERVE INJURY 603

DIAGNOSING NERVE INJURY 604

History and Physical Examination 604

Vascular Testing 604

Neurologic Testing 604

GENERAL PRINCIPLES OF TREATMENT 604

Ischemic Neuropathy 604

Trauma 604

SPECIFIC NERVE INJURIES 605

Nerve Injuries with Exposure of Extracranial Carotid Artery 605

Nerve Injuries with Supraclavicular and Thoracotomy Exposures 605

Brachial Plexus and Upper Extremity Nerve Injuries 605

Superior Hypogastric Plexus and Hypogastric Nerve Injury 605

Lumbosacral Plexus Injuries 610

Lower Extremity Nerve Injuries 610

CHAPTER ALGORITHM 612

INTRODUCTION

Nerves are complex in formation, surrounded by Schwann cells as the conductive myelin sheath with a supportive structure of extracellular matrix and vasculature. Smaller nerves are simpler, without such supportive structure, relying on diffusion through the interstitial space to supply their metabolic demands. Interestingly, the oxygen requirement of a mammalian nerve is less than that of other tissues, even with increased metabolism.¹ In other words, nerves are inherently resistant to ischemia. The larger nerves of the extremities contain multiple networks of vessels supplied by branches of adjacent arteries, while the inner portions of the nerves contain an extensive pattern of epineurial vessels.^{2,3} Interruption of the blood supply to a segmental portion of the nerve usually does not result in ischemic nerve injury.^{4,5} One notable exception is ischemic monomelic neuropathy (IMN), an infrequent ischemic nerve injury following acute limb malperfusion, which is characterized by multiple distal axonal infarctions and resultant motor and sensory mononeuropathies.^{6,7}

There are two functional components of the peripheral nervous system. The *somatic system* is composed of motor and sensory fibers acting together to allow for muscle contraction and sensory function. Cranial and spinal nerves of the somatic

system are composed of a ventral (motor) and dorsal (sensory) root. While the first two pairs of cranial nerves (the olfactory nerve and the optic nerve) originate from the cerebrum and are not a part of the peripheral nervous system, the other ten cranial nerves originate from the brain stem and enter the peripheral nervous system after leaving their associated nuclei. Along the spine, there are 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 pair of coccygeal nerves.

The *autonomic system* is composed of sympathetic and parasympathetic fibers working without conscious control innervating organs. The sympathetic nervous system prepares the body for “fight or flight” response. The main neurotransmitters of the autonomic system released are acetylcholine and norepinephrine. The parasympathetic nervous system has digestive and elimination function. The main neurotransmitter released by the pathway is also acetylcholine.

ISCHEMIC NEUROPATHY

The true incidence of ischemic neuropathy is difficult to determine. Symptoms of ischemic nerve injury may mimic rest pain associated with arterial insufficiency or decreased sensation due to diabetic neuropathy. Historically, the incidence of ischemic

neuropathy associated with PAD has been estimated to be as high as 88%.⁸ This has been confirmed in contemporary studies reporting a similar incidence of nerve dysfunction detectable by electrophysiologic nerve conduction studies.^{8–12} Both acute and chronic ischemic conditions have the potential to cause nerve injury, however the mechanism of ischemic neuropathy specific to PAD has not been fully elucidated.

Acute Ischemic Neuropathy

Animal models of acute limb ischemia demonstrate that injured mammalian nerve can recover after short periods of ischemia following occlusion of large inflow arteries¹³ and smaller vasa nervorum.¹⁴ There exists a certain time threshold (6–10 hours) beyond which the neurologic damage is irreversible.^{15,16} Peripheral nerve tissue initially recruits oxygen and nutrient supply from the surrounding interstitial fluid. The rich collateral circulation within the nerve bundle itself is also protective against ischemic nerve injury. Persistent hypoxemia and hypercapnia lead to hyperkalemia and acidosis, which in the local milieu may contribute to irreversible depolarization of the axon cell membrane.^{17,18} Exactly how much ischemia the human peripheral nerve is able to tolerate without irreversible injury is still unknown.

Ischemic monomelic neuropathy (IMN) is a subcategory of acute neuropathy most frequently diagnosed in patients undergoing hemodialysis access placement involving the brachial artery. The diagnosis, made after exclusion of arterial steal syndrome and direct nerve compression, is uncommon and can be confounded by the presence of diabetic or uremic neuropathy in patients. The pathophysiology of IMN does not result in the characteristic Wallerian degeneration seen in other nerve injuries, where fragmentation of both the axon and myelin are early responses. Nerve biopsies following IMN will not display axonal degeneration and demyelination.¹⁹ It is believed that altered blood flow through the vasa nervorum causes acute but reversible conduction block. Persistent malperfusion leads to distal axonal infarction and manifests as multiple axonal-loss mononeuropathies in the extremity.²⁰ IMN has been proposed to result from acute ischemia superimposed on predisposing factors such as diabetic neuropathy and peripheral vascular disease. Prompt recognition of IMN after arteriovenous fistula or graft placement with revision or ligation of the newly created access is essential. Recovery function and relief of pain is variable following access revision, and in some individuals, sensory and motor deficits may be prolonged and permanent.

Chronic Ischemic Neuropathy

Researchers have focused on using histologic findings of peripheral nerve specimens obtained from patients with chronic PAD to study chronic ischemic neuropathy. These specimens show segmental demyelination and remyelination, as well as axonal degeneration and regeneration.⁸ The mechanism by which chronic limb ischemia produces changes in the peripheral nerve is still not known. Similar morphologic changes in peripheral nerves were observed following both acute and

chronic ischemia suggesting that the lack of blood flow and oxygen delivery have the same effect when present acutely or over time.²¹ The severity of the chronic ischemia so far has not been shown to correlate with the degree of histologic damage found in peripheral nerves.²² Furthermore, Lacroix et al.²³ suggest the injury observed in chronically ischemic limbs may not be a result of slow progression of the ischemic process but rather the accumulation of multiple repeated episodes of acute ischemia. This is supported by more recent evidence that ischemic preconditioning, which can be beneficial to skeletal muscle tissue, is harmful to peripheral nerve tissue.²⁴

TRAUMATIC NERVE INJURIES

Peripheral nerves in proximity to major arteries and veins are at risk for iatrogenic injury during vascular interventions. Without a commanding knowledge of the anatomic relationships of structures, vascular surgeons may successfully restore flow to an extremity yet leave significant neurologic deficits because of surgical trauma. Fortunately, most peripheral nerve injuries that occur during operative exposure result in transient nerve dysfunction (neurapraxia) that recovers with time.

Traumatic injury occurs via several mechanisms. Division or ligation of a nerve renders the nerve permanently damaged. Reconstruction of divided nerves is possible with acceptable rates of functional recovery but the outcome is variable.^{25–29} Other mechanisms include stretch injury from improper retractor placement, thermal injury from electrocautery devices and compressive injury from hematoma formation or from improper patient positioning. Avoiding nerve injury requires constant vigilance for anatomic relationships and technical precision. Except in the case of severance, the peripheral nerves have remarkable capacity to regenerate and functional outcomes, in most instances, is favorable.^{29–31}

OTHER CAUSES OF NERVE INJURY

Some patients evaluated will have peripheral neuropathy not due to ischemia or trauma. Other causes of neuropathy should be included in the differential diagnosis (Table 47.1). Diabetic neuropathy is the most commonly encountered alternative cause of peripheral neuropathy seen by vascular specialists.³² Risk factors include increasing age, length of diabetes diagnosis, poor glycemic control, poor lipid metabolism, inadequate blood pressure control, obesity, and metabolic syndrome.^{32–34} The etiology of the nerve damage is multifactorial and not completely understood. The metabolic derangements associated with chronically elevated blood glucose levels and abnormal insulin homeostasis are thought to be the major determinants.³⁵ Vascular disease in the microcirculation is also believed to play a role in nerve damage, thus making the difference between diabetic neuropathy and ischemic neuropathy less distinct.³⁶ Other causes of peripheral neuropathy include alcoholism, uremia, drug intoxication, medication side effects, vasculitis, autoimmune disorders, infectious causes, and inflammatory causes. Most often, these associated neuropathies are symmetric.

TABLE 47.1**Examples of Common Types of Neuropathy: Causes**

Commonly Unilateral
• Entrapment
• Trauma
• Ischemia
• Vasculitis
Commonly Bilateral
• Metabolic (diabetes, uremia)
• Toxic (alcohol, drugs, metal)
• Connective tissue disease, vasculitis
• Deficiency (vitamin)
• Inflammatory
• Monoclonal gammopathies
• Human immunodeficiency virus infection

DIAGNOSING NERVE INJURY**History and Physical Examination**

Neuropathy in the lower extremity may be accompanied by slight ankle weakness and depressed reflexes. There is unilateral sensory loss in a “stocking” distribution, particularly affecting vibratory sense. The small muscles of the affected foot may become atrophied. After revascularization of a severely ischemic limb, persistent pain due to neuropathy may continue to be present. The neuropathic pain is burning and paresthetic, is worse with rest and at night, and is not relieved by walking. The patient with neuropathy may perceive the foot to be cold although it is warm and remark on stiffness or loss of mobility of the toes. Ischemic rest pain associated with arterial insufficiency, in contrast, is relieved to some extent by placing the limb in the dependent position and generally is cooler compared to adequately perfused limbs.

Vascular Testing

Ankle pressure <40 mm Hg or toe pressure <30 mm Hg suggests inadequate peripheral circulation. Monophasic Doppler waveforms also indicate severe arterial insufficiency (see Ch. 21, Vascular Laboratory: Arterial Physiologic Assessment). When perfusion is inadequate, the pain may be due to arterial insufficiency, neuropathy, or both, but treatment should be directed first toward improvement of limb blood flow. If arterial insufficiency is present, efforts should be made to revascularize in parallel with any indicated neurologic testing. A neurologic evaluation should be performed if no arterial insufficiency is present.

Neurologic Testing

Electrophysiologic testing can establish the diagnosis and severity of neuropathy. With ischemic neuropathy, patients

typically have a unilateral axonal neuropathy involving the distal tibial and peroneal nerves. Motor nerve conduction studies show decreased or absent compound muscle action potential amplitude following nerve stimulation in the affected foot.³⁷ Distal latency and the velocity of conduction in the calf portion of these nerves are relatively well preserved. These findings are in sharp contrast to diabetic and uremic neuropathy, where distal latencies and conduction velocities tend to be reduced below normal velocities at an early stage, and in a bilateral, symmetrical pattern.

Sensory nerve conduction studies in ischemic neuropathy show decreased or absent sensory potential amplitudes from the sural, superficial peroneal and plantar nerves, whereas sensory conduction velocity, when recordable, is normal.^{37,38} Needle electrode examination reveals muscle denervation in the small muscles of the affected foot, particularly in the sole of the foot, with fibrillation potentials at rest and large motor units of long duration in much reduced numbers.

GENERAL PRINCIPLES OF TREATMENT**Ischemic Neuropathy**

If a patient has acute arterial ischemia, in addition to acute ischemic neuropathy, revascularization will often improve the motor and sensory symptoms of ischemic neuropathy either immediately or during the first few postoperative weeks. Chronic ischemic neuropathy is less likely to improve with revascularization. If symptoms persist and revascularization of the limb is deemed adequate, other potential causes of neuropathy should be excluded.

Referral to a neurologist can be helpful for neuropathy diagnosis and treatment. Treating the pain of neuropathy, particularly ischemic neuropathy, is often difficult because narcotic regimens used for postsurgical pain may not be effective and anti-inflammatory drugs are generally ineffective. First-line therapy may include tricyclic antidepressants (TCAs) or selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). Secondary amine TCAs (nortriptyline and desipramine) are generally better tolerated in the elderly than tertiary amine TCAs (amitriptyline and imipramine), however all TCAs have potential cardiac toxicity and should be avoided in patients with ischemic heart disease.³⁹ SSNRIs (duloxetine and venlafaxine) have a more favorable side-effect profile and less risk of cardiac toxicity, but analgesic efficacy is inconsistent.³⁹ Calcium channel α 2- δ ligands (gabapentin and pregabalin) are also used for first-line therapy, but do not provide reliable relief for all patients. The most common dose-limiting side effects include somnolence and dizziness, and renal insufficiency requires dose reduction. Although well tolerated if titrated properly, it may take weeks to establish effective dosage.³⁹

Trauma

Partial loss of nerve function after surgery will generally recover since nerves have the ability to regenerate. The rate of axonal regeneration is estimated to be 1 mm per day, and therefore,

the recovery period may be lengthy.¹⁹ In a patient with severe loss of motor and sensory function, surgical re-exploration should be considered. If a major nerve or branch is found to be divided, repair is indicated. If a nerve is acutely compressed because of a hematoma, surgical decompression should be performed promptly and will often result in recovery of function. In cases in which symptoms persist without signs of healing and nerve conduction studies indicate loss of nerve function, surgical exploration with neurolysis and nerve grafting offers some hope of recovery of function, with encouraging results being reported in contemporary series.^{26–31}

SPECIFIC NERVE INJURIES

Nerve Injuries with Exposure of Extracranial Carotid Artery

Table 47.2 lists the most commonly injured cranial nerves during exposure of the extracranial carotid artery (see Ch. 93, Carotid Endarterectomy). In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), cranial nerve injury was reported in 4.6% of patients undergoing carotid endarterectomy (CEA) with an 80% resolution rate at one year.⁴⁵ Kakisis et al. performed a meta-analysis reviewing published studies reporting cranial nerve injuries with CEA and reported the vagus nerve to be the most frequently injured while others have reported the hypoglossal nerve to be the most frequently injured.^{46–49} In addition to CEA, the cranial nerves can be injured with penetrating injury, compression from aneurysms or hematomas, ischemia or compression from arterial dissections, or other rare causes including arteriovenous malformations and brainstem cavernomas.

Nerve Injuries with Supraclavicular and Thoracotomy Exposures

Table 47.3 lists the most commonly injured nerves in the supraclavicular space and chest wall. These nerves can be injured during the exposure of the carotid, subclavian, and axillary vessels with revascularization, decompression of the thoracic outlet and thoracotomy procedures.

Brachial Plexus and Upper Extremity Nerve Injuries

The brachial plexus, comprised of cervical (C) and thoracic (T) roots, gives rise to the five main terminal nerves of the upper extremity: the axillary nerve (C-5, C-6), the musculocutaneous nerve (C-5, C-6), the median nerve (C-5–T-1), the radial nerve (C-5–C-8), and the ulnar nerve (C-8, T-1). In the supraclavicular space, the nerve roots of the plexus combine into three trunks: superior, middle and inferior. These trunks are intimately associated with the distal subclavian and proximal axillary artery. Underneath the clavicle, the trunks divide into three cords: lateral, posterior and medial. The axillary artery is lateral to the medial cord and anterior to the posterior cord.

The major peripheral nerves originate towards the distal portion of the axillary artery. The median nerve lies anteriorly, the ulnar nerve lies medially, and the radial nerve lies posteriorly to the axillary artery (Fig. 47.1).

Clavicular and proximal humeral fractures, as well as penetrating injuries, can result in hematomas, transection or pseudoaneurysms of the distal subclavian and axillary artery with compression of the brachial plexus. The upper extremity is so well vascularized that patients presenting with such injuries might have palpable distal pulses. Hematomas in the neurovascular bundle or fascial compartments of the upper extremity can compress associated nerves and predispose the arm to peripheral neuropathy.⁵³ Prompt surgical decompression of any post-procedural hematoma causing neurologic symptoms in the upper extremity may prevent permanent nerve damage.^{54,55} In patients with a delayed diagnosis, the benefit of intervention decreases; however, operative reconstruction of traumatically injured nerves within three months of injury has shown acceptable rates of motor and sensory recovery.⁵⁶ Upper extremity neuropathies involving the brachial plexus can also result from patient malpositioning. These manifest in the immediate post-procedural period as motor and sensory deficits. Table 47.4 describes the most commonly encountered nerves in the upper extremity that can be injured with surgical intervention. The locations of the upper arm and forearm nerves are depicted in Figures 47.2 and 47.3, respectively.

Superior Hypogastric Plexus and Hypogastric Nerve Injury

The superior hypogastric plexus, also known as the pre-aortic plexus, is composed of lumbar (L) and sacral (S) nerve roots (L-4 through S-1), lying anterior and caudal to the aortic bifurcation, slightly left of the midsagittal plane. The plexus branches into two hypogastric nerves, which originate at the level of the sacral promontory and run medial to the ureters. The right hypogastric nerve is generally smaller. The superior hypogastric plexus is the main efferent sympathetic innervation to the bladder neck, vas deferens and prostate and is responsible for ejaculatory function.

Interruption of the superior hypogastric plexus or the hypogastric nerves can lead to erectile dysfunction and retrograde ejaculation. These are potential complications associated with aortoiliac reconstructive surgery for both aortoiliac occlusive and aneurysmal disease. This complication can occur in as many as 49% to 63% of male patients undergoing aortic surgery⁶⁵ (see Ch. 191, Erectile Dysfunction).

To minimize sexual dysfunction, unilateral preservation of the superior hypogastric plexus and hypogastric nerves is recommended with disruption, if necessary, of the right side suggested.⁶⁶ For aorto-bi-iliac and aorto-bifemoral reconstructions, the initial incision should be made within 1 cm distally on the right common iliac artery and extended up proximally onto the right side of the aorta to the level of the left renal vein. The left common iliac artery should be incised separately approximately 4 cm below the aortic bifurcation and the left limb of the bypass graft should be tunneled underneath the plexus.

TABLE 47.2 Nerves Injured with Extracranial Carotid Artery Exposure

Nerve	Origin	Notable Branches	Location	When Injury Occurs	Resulting Deficit	Comments
Vagus n.	CN X		In carotid sheath, between IJV and CCA	Forceful retraction, passing-pointing with clamp tips	Hoarseness, loss of effective cough, paralysis of ipsilateral vocal cord	Perform preoperative laryngoscopy to assess vocal cord function if undergoing contralateral CEA
		External branch of superior laryngeal n.	Medial to superior thyroid a.		Unable to produce high-pitched tones (cricothyroid m.)	
		Recurrent laryngeal n.	Left wraps around aortic arch Right wraps around subclavian a.	Dissection close to trachea, forceful retraction	Hoarseness, ipsilateral vocal cord paralysis	Injury can affect up to 7% of CEA procedures ⁴⁰ Nonrecurrent right crosses the distal CCA, present in 0.3%–0.8% of population ⁴¹
Hypoglossal n.	CN XII		Crosses the ICA and ECA 2 cm above bifurcation, occipital a. sling	High exposure of ICA	Deviation of the tongue to the ipsilateral side, dysphagia and speech impediment	
Marginal mandibular n.	CN VII		Below the platysma, 1 cm caudal to the mandible	Incisions made close to the jawline, forceful retraction	Sagging of ipsilateral mouth corner, paralysis of lower lip when asked to show teeth	Prevented by curving the superior aspect of incision towards mastoid, intermittent release of retraction
Glossopharyngeal n.	CN IX		Adjacent to stylohyoid ligament	High ICA exposure, division of the digastric m., subluxation of the mandible, detachment of the styloid process	Paralysis of the pharyngeal constrictor m. leading to loss of gag reflex and dysphagia ⁴²	Rare
		Nerve of Herring/ carotid sinus	Branch point of the ICA and ECA			Injected with lidocaine to prevent bradycardia or hypotension with manipulation
		Ascending fibers of glossopharyngeal n.			Horner syndrome with ipsilateral ptosis, miosis and anhidrosis	The incidence of Horner syndrome with CEA is 3.8%, with 1.9% lasting 12 months ⁴³
Spinal accessory n.	CN XI		Identified anterior to the IJV	Sternocleidomastoid m. retraction	Ipsilateral shoulder droop, atrophy of the trapezius m. and winged scapula	Rarely injured with CEA ⁴⁴
Great auricular n.	CN VII		Superior aspect of the CEA incision, below the ear, anterior to sternocleidomastoid m.		Numbness around the ear and scalp, ipsilateral occipital headache	

Abbreviations: a., artery; CCA, common carotid artery; CEA, carotid endarterectomy; CN, cranial nerve; ECA, external carotid artery; ICA, internal carotid artery; IJV, internal jugular vein; m., muscle; n., nerve.

TABLE 47.3 Nerves Injured in the Supraclavicular Space and with Thoracotomy Exposures

Nerve	Origin	Location	When Injury Occurs	Resulting Deficit	Comments
Phrenic n.	C-3, C-4, and C-5 cervical roots	Above the clavicle, courses over the anterior scalene m. and subclavian a. Below clavicle (right), runs lateral to the SVC, adjacent to the right heart and lung root, through the IVC hiatus, to the dome of the right hemidiaphragm Below clavicle (left), runs over the aortic arch and anterior to the left heart, pierces the left dome of the hemidiaphragm to enter the abdomen Within the diaphragm, runs radially with anterior, lateral and posterior branches	Exposure of the subclavian a., detachment or debulking the anterior scalene m. Aneurysmal degeneration of the aorta and injury with endovascular and open thoracic exposures can lead to phrenic n. palsy ⁵⁰ Open thoracoabdominal aortic exposure with division of the diaphragm	Shortness of breath, recurrent PNA, hemi-diaphragmatic elevation	Diagnosed with the fluoroscopic sniff test demonstrating ipsilateral paradoxical elevation with inspiration and paradoxical depression on expiration ⁵¹ Can be avoided with circumferential, not radial, division of the diaphragm
Long Thoracic n.	C-5, C-6, and C-7 cervical roots	Pierces the middle scalene m.		Palsy of the serratus anterior m. with winged scapula, difficulty lifting upper extremity overhead	
Intercostal n.	Anterior division of thoracic nerve roots T-1 through T-11	Paired nerves (left and right) travel within the corresponding intercostal space, as it courses anteriorly nerve lies inferior to the rib	Thoracotomy exposures with incision, retraction, rib removal and closure	Intercostal neuralgia (neuropathic pain in the associated area)	Chronic pain associated with thoracotomy was 61% at 1 year ⁵²

Abbreviations: C, cervical root; IVC, inferior vena cava; PNA, pneumonia; SVC, superior vena cava; T, thoracic root.

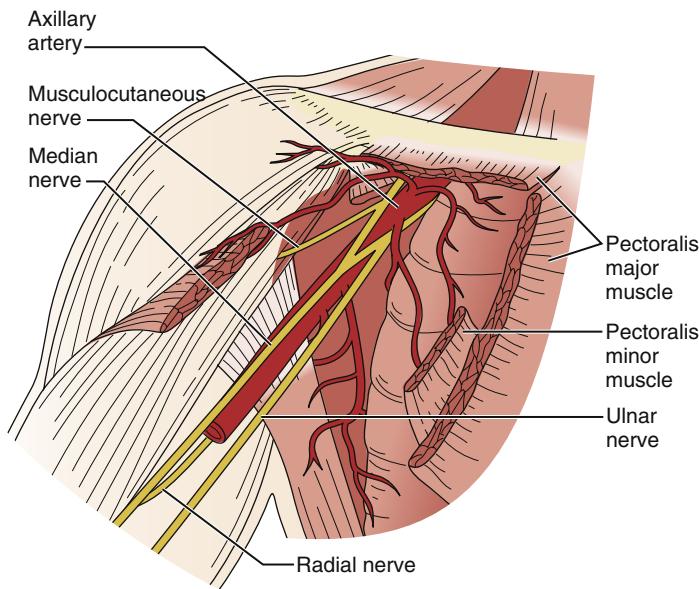


Figure 47.1 Relationship of the axillary artery to the brachial plexus nerves.

Ligation of the inferior mesenteric artery from the inside of the aortic sac is also recommended to prevent injury to the inferior mesenteric plexus. The inferior mesenteric plexus is one of the origins of the superior hypogastric plexus and disruption can

also lead to sexual dysfunction (see Ch. 56, Abdominal Vascular Exposures).

Sexual dysfunction after endovascular aortic aneurysm repair is also prevalent. In a meta-analysis of 29 studies, Regnier

TABLE 47.4 Nerves Injured with Exposure of the Brachial Plexus and Upper Extremity

Nerve	Origin	Location	When Injury Occurs	Resulting Deficit	Comments
Median n. (Proximal)	Medial and lateral cords of BP	Antecubital fossa, deep to bicipital aponeurosis, anteromedial to brachial a. between two heads of pronator teres m.	Brachial a. catheterization, brachial sheath hematomas and pseudoaneurysms, creation of dialysis access	Patients unable to pinch thumb and forefinger, "Orator's sign"	Nerve injury during brachial artery catheterizations has been reported in 0.2% to 1.4% of patients ⁵⁷
Median n. (Distal)	Medial and lateral cords of BP	At the wrist, under flexor retinaculum	Forearm and hand fasciotomies	Decreased sensation over thenar eminence, palmar surface, thumb and forefinger	Chronic injury is carpal tunnel syndrome
Ulnar n.	Medial cord of the BP, nerve roots C-8 and T-1	Proximal upper arm, posterior to the basilic v., medial to the axillary and brachial a. Distal upper arm, posteromedial aspect of the humerus Forearm, adjacent to the ulnar artery	Circumferential exposure of the basilic v. in the upper arm ⁵⁸ Exposure of the ulnar a. in the forearm Positioning with extreme elbow flexion and pronation, medial epicondyle pressure	Numbness of the fifth and fourth digits, weakness of the hypothenar muscles, abduction and adduction of all digits	
Medial antebrachial cutaneous n.	Medial cord of the BP, C-8 and T-1 nerve roots	Anterior to the basilic v. in the upper arm, divides into anterior and posterior divisions 10 cm proximal to medial epicondyle	Dialysis access creation, transposition and superficialization, repeated injury with dialysis access	Numbness or pain of medial elbow or forearm	Division of the perineurium to elevate the basilic v. between the nerve branches without transection ⁵⁹
Radial n. (Proximal)	Posterior cord of the BP, C-5 to T-1 nerve roots	Proximal upper arm, runs posterior and lateral to the humerus Distal upper arm, anterior around the lateral epicondyle of the humerus	Humeral fractures or shoulder dislocations, hematomas, pseudoaneurysms or other compressive forces in the axilla	Patient may hold the affected hand with the contralateral hand, wrist drop, weakness of wrist and finger extension	
Superficial branch of radial n. (Distal)	Posterior cord of the BP, C-5 to T-1 nerve roots	Runs in the subcutaneous tissue with the cephalic v.	Can be injured with venipuncture, radiocephalic arteriovenous fistula creation, radial artery punctures, radial artery harvest for coronary artery bypass grafting	Numbness over dorsal hand	Trans-radial coronary artery catheterization may be associated with injury of the superficial radial nerve. ^{60,61} Neurovascular deficits after radial a. harvest usually resolve with time, equal injury rates between electrocautery and sharp dissection ⁶²⁻⁶⁴

Abbreviations: BP, brachial plexus; C, cervical nerve root; T, thoracic nerve root.

et al. evaluated the incidence of sexual dysfunction after both open and endovascular repair for abdominal aortic aneurysms. The incidence associated with open repair ranged from 7.4% to 79% while the incidence associated with endovascular repair ranged from 4.7% to 82%. Erectile dysfunction occurred in 5.3% to 8.2% of cases with unilateral iliac artery exclusion and 5.1% to 46.6% of cases with bilateral iliac artery occlusion.⁶⁷ Recommendations to prevent pelvic ischemia include staging

endovascular repair of abdominal aortic aneurysms if requiring coil embolization of the internal iliac artery, coil embolization as close to the internal iliac artery origin to allow for persistence of the ipsilateral pelvic circulation, and preservation of collaterals from the ipsilateral femoral artery. Finally, branched stent grafts for preservation of the internal iliac artery and open surgical bypass are additional options to maintain pelvic circulation.

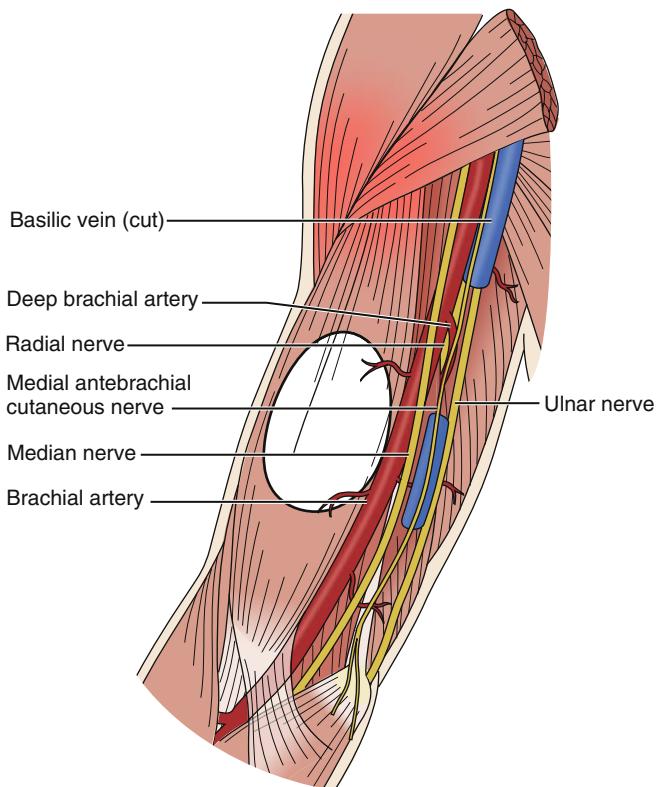


Figure 47.2 Relationship of the brachial artery and basilic vein to the median and ulnar nerves in the neurovascular bundle that runs deep to the medial brachial fascia.

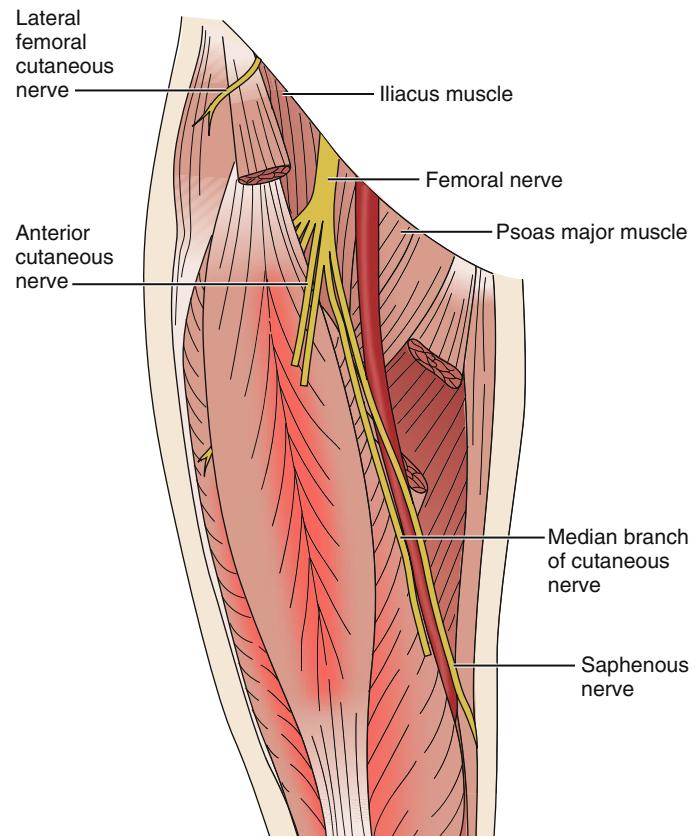


Figure 47.4 Anatomy of the femoral nerve.

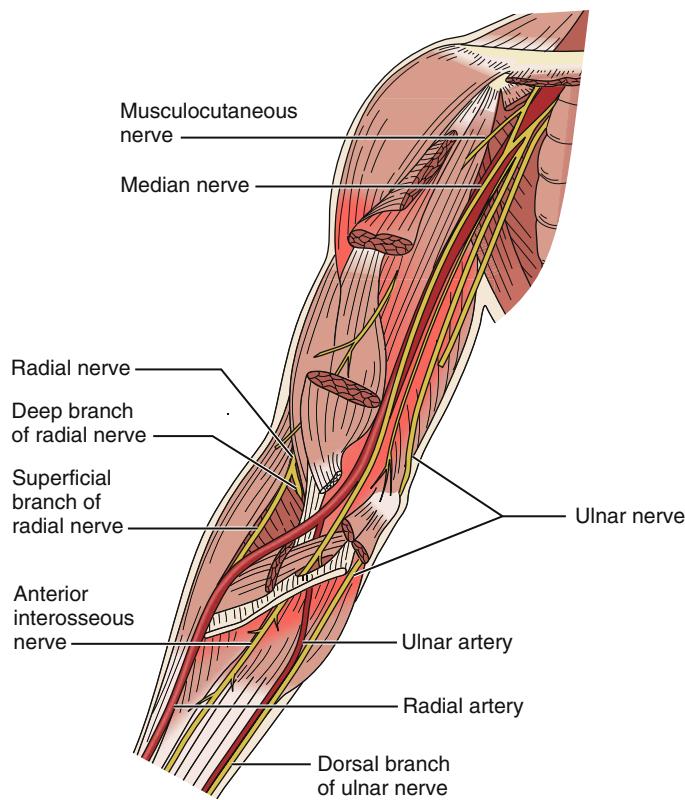


Figure 47.3 Relationship of named arteries and nerves of the upper extremity. Note that the ulnar nerve and ulnar artery are in close proximity at the wrist.

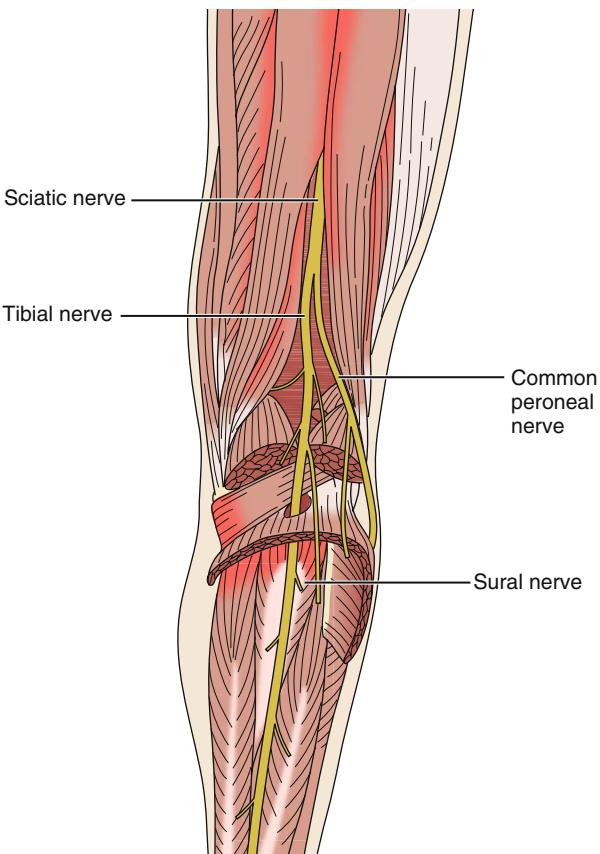


Figure 47.5 Anatomy of the sciatic, tibial, sural, and peroneal nerves.

Lumbosacral Plexus Injuries

The lumbosacral plexus consists of lumbar and sacral nerve roots joined together by a lumbosacral trunk originating from L-4 and L-5. The lumbar plexus is comprised of T-12 through L-4 nerve roots. The sacral plexus consists of the lumbosacral trunk and S-1, S-2 and S-3 nerve roots. Blood supply to the lumbosacral plexus is through five sets of paired lumbar arteries arising from the abdominal aorta, the deep circumflex iliac arteries (branches of the external iliac arteries), and the iliolumbar and gluteal branches of the internal iliac arteries.

The lumbar plexus is largely in the body of the psoas muscle and provides the terminal nerves responsible for hip flexion, knee extension, leg adduction and sensation for the lower abdomen, upper buttock, upper and medial thigh, and medial leg. The terminal nerves derived from the lumbar plexus include the femoral, obturator, ilio-inguinal, ilio-hypogastric, genitofemoral and lateral femoral cutaneous nerves.

The sacral plexus is responsible for hip extension, abduction, knee flexion, foot and digital dorsi- and plantar-flexion, as well as sensation for the posterior thigh and anterior, lateral and posterior leg. Terminal nerves derived from the sacral plexus include the sciatic, pudendal, posterior femoral cutaneous and terminal nerves to the muscles of the pelvic floor.

The majority of lumbosacral plexus injuries occur with total hip replacements, gynecologic and urologic procedures but injuries to the lumbosacral plexus resulting from vascular surgery can occur in the setting of high retroperitoneal exposures with dissection, traction and ischemia with aortoiliac interventions. Exposure of the iliac arteries may require dissection and retraction of structures in the iliac fossa, with a corresponding risk of injury to the nerves coursing along the psoas major muscle. Improper positioning of retractors (especially self-retaining devices) can lead to significant blunt injury to these nerve branches.

Lumbosacral plexus neuropathy after aorto-bi-femoral bypass grafting for aneurysm disease was described in 1970, evidenced by infarction of the plexus found on autopsy.⁶⁸ More recently, similar findings after open and endovascular aortoiliac procedures suggest that thrombosis of the internal iliac artery might play a causal role in the ischemic nerve injury.⁶⁹ The incidence of lumbosacral plexus injury after open aortoiliac operations may be as low as 0.3%, presumably secondary to pelvic ischemia, but the true incidence and risk factors remain ill-defined.^{70–72} Case reports of lumbosacral nerve root injury have been reported after endovascular stent-graft repair of the abdominal aorta, with some authors reporting a lower incidence of nerve complications with endovascular repair compared to open repair.^{73–75} Other causes of lumbosacral plexus injury include acute compression from a retroperitoneal

hematoma or chronic compression from iliac artery aneurysm or pseudoaneurysm.^{76–78}

Both lumbosacral plexus and lower spinal cord injury can result from iatrogenic injury and traumatic events and differentiating between the two pathologies is crucial. Careful history and physical examination will reveal the level of injury. Injury to the lumbosacral plexus most commonly produces unilateral motor and sensory loss and affects more than one dermatomal segment, unlike an injury in a peripheral nerve, which has a unique sensory and motor distribution. The weakness associated with a plexus injury may be in both the large proximal muscle groups and the smaller distal muscle groups, with flaccid paralysis, absence of reflexes, and a sensory deficit to pain, temperature, and vibration. Spinal cord injuries produce unilateral or bilateral dysfunction and spastic, hyper-reflexic limbs with varying degrees of hip, knee, and ankle flexor weakness, along with an extensor plantar response. Typically, with an ischemic cord lesion, there is an identifiable sensory level deficit to pain and temperature, with preservation of position and vibration sense.

On electromyography, a lumbosacral plexus neuropathy will manifest as unilateral loss of sensory potentials, reduced motor conduction, absent paraspinal denervation, and the presence of denervation changes in muscles innervated by multiple nerves and roots. In spinal cord injuries, nerve conduction studies are normal, and there are no denervation changes.

Overall, there is some evidence to suggest that lumbosacral plexus injury has a better prognosis than spinal cord injury, but definitive studies are lacking.⁷⁰ If the etiology can be determined, intervention may result in regaining nerve function. In the case of compression from hematoma or aneurysm, relief of the compression in the early stages of nerve dysfunction may improve the long-term outcome.^{76–78} For nerves with ischemic injury, the likelihood of restoring nerve function with correction of the ischemia is less likely.

Lower Extremity Nerve Injuries

Open surgical revascularization for the treatment of peripheral arterial disease requires a thorough understanding of the anatomy of the nerves of lower extremities. Figures 47.4 and 47.5 depict the location of the lower extremity nerves in the groin and lower leg. Depending on the patient's need for revascularization and the operative exposure, multiple nerve injuries can occur. Table 47.5 includes many of the most commonly injured lower extremity nerves. While many presentations of lower extremity nerve injury can be subtle, many can leave the patient with a dysfunctional gait and life-long disability (see Ch. 58, Lower Extremity Arterial Exposure).

TABLE 47.5 Nerves Injured with Surgical Exposure of the Lower Extremity

Nerve	Origin	Location	When Injury Occurs	Resulting Deficit	Comments
Lateral femoral cutaneous n.	L-2, L-3 and L-4 nerve roots Does not originate from the femoral n.	Runs lateral to psoas and iliacus m., under the IL, anteromedial to sartorius m., pierces the tensor fascia lata	Iatrogenic injury with lumbar spine surgery Retroperitoneal bleeding, hematomas and masses	Thigh and buttock paresthesias, weakness of hip flexion and knee extension	Relationship to ASIS is variable Meralgia paresthetica is entrapment of the nerve underneath IL, seen in obese, diabetics, alcoholics and runners
Obturator n.	Anterior divisions of L-2, L-3 and L-4	Travels through the psoas, exits along the lateral pelvic wall, superior and lateral in the obturator membrane	Neuropathy with obturator and femoral a. aneurysms Injured with obturator bypass and femoral a. procedures	Numbness of medial thigh and weakness of thigh adduction	Obturator membrane should be sharply incised on the anteromedial aspect to avoid injury
Femoral n.	L-2, L-3, L-4 nerve roots	Descends through the psoas m. into the iliacus groove, under the IL lateral to the femoral a., divides into anterior and posterior divisions at the lateral circumflex a.	Use of self-retaining retractors during pelvic surgery Prolonged, hyperflexed lower extremities, re-operative groin surgery, compression by groin hematomas or pseudoaneurysms	Diminished extension of the knee, and reduced patellar reflex	Redundant blood supply from deep circumflex iliac, iliolumbar and lateral circumflex femoral a. protects from ischemic injury ⁴
Anterior cutaneous femoral n.	Anterior division of femoral n.	Multiple muscular and sensory branches in the thigh	Dissection of the femoral vessels within the femoral triangle, re-operative groin surgery	Anterior thigh pain and numbness	Pain associated with injury can resolve with conservative measures
Saphenous n.	Femoral n. branch, L-3 and L-4 nerve roots	In the thigh, runs adjacent to superficial femoral a., through the adductor canal, runs more superficial medial to the tibial tuberosity and adjacent to the GSV	Associated sensory loss after popliteal a. exposure and GSV harvest (up to 12.5% with endoscopic harvest for CABG) High injury rate with venous ablation and stripping procedures with 58% injury with neurologic testing	Paresthesias, anteromedial thigh, medial lower leg and ankle	Less injury associated with GSV treatment only to the level of the knee Decreased incidence of injury and duration of paresthesias with EVLT compared to RFA
Sural n.	Tibial n. branch, S-1 and S-2 nerve roots	Exits the popliteal fossa, runs between the two heads of the gastrocnemius m., courses lateral to the SSV Communicating peroneal n. branch joins the sural n. in the mid-calf and runs to the lateral malleolus	At risk for injury with SSV harvest or stripping, and saphenopopliteal exposure	Paresthesias in the posterior calf or lateral ankle	Patients with sural nerve injury may develop an unbearable chronic pain syndrome
Sciatic n.	Anterior roots of L-4, L-5, S-1, S-2 and S-3	Exits pelvis through the greater sciatic foramen below the piriformis m., runs in posterior thigh between the ischial tuberosity and the greater trochanter	Injury can result from high lithotomy positioning with thighs flexed more than 90° Can be injured with total hip replacement	Injury can result in foot drop	Rarely, sciatic n. ischemic injury has been recognized in cardiac surgery patients with PAD
Tibial n.	Medial division of the sciatic n., L-4, L-5, S-1, S-2 and S-3 nerve roots	Travels with the popliteal a. into the lower leg, in the posterior deep compartment	Posterior knee dislocation can involve the tibial or peroneal n. and should be explored if compression is expected The neurologic dysfunction associated with ACS recovers quickly with prompt decompression	Weakness of ankle and toe plantar flexion, sensory loss on the sole and lateral aspect of the foot	Traumatic injury to both the popliteal artery and tibial n. is associated with a 3-fold higher risk of lower extremity amputation

Continued

TABLE 47.5

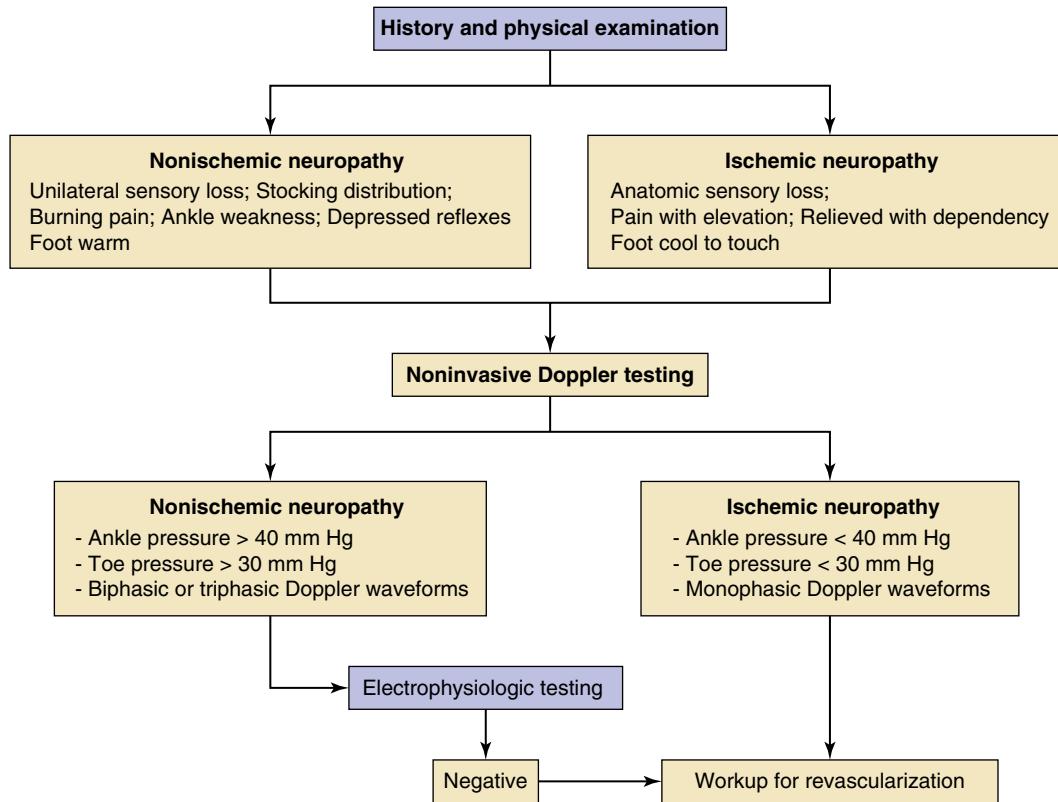
Nerves Injured with Surgical Exposure of the Lower Extremity—cont'd

Nerve	Origin	Location	When Injury Occurs	Resulting Deficit	Comments
Peroneal n.	Sciatic n. branch, L-4, L-5, S-1, S-2 and S-3 nerve roots	Runs through posterior thigh, lateral popliteal fossa, around to the fibula head, divides into superficial and deep branches in the lower leg Superficial peroneal n. runs in the lateral compartment without an associated artery Deep peroneal n. enters the anterior compartment and along the intermuscular septum with the anterior tibial vessels	Peroneal n. injury is reported with posterior knee dislocation, total knee arthroplasty, SSV ablation and with harvest when the saphenopopliteal junction is abnormally high Superficial peroneal n. can be compressed with operative positioning if not properly padded Deep peroneal n. is at risk for injury with ACS	Weakness of ankle and toe dorsiflexion (foot drop), loss of sensation in the lateral calf, dorsal foot and toes	Traumatic injury to the peroneal n. warrants surgical exploration if functional loss is complete or if compression is suspected

Abbreviations: ACS, acute compartment syndrome; ASIS, anterior superior iliac spine; CABG, coronary artery bypass grafting; EVLT, endovascular laser treatment; GSV, great saphenous vein; IL, inguinal ligament; L, lumbar nerve root; PAD, peripheral arterial occlusive disease; RFA, radiofrequency ablation; S, sacral nerve root; SSV, small saphenous vein; VV, varicose veins.

CHAPTER ALGORITHM

Diagnostic algorithm: Ischemic vs. nonischemic neuropathy



SELECTED KEY REFERENCES

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This important animal study examines the role of TNF-alpha and the effect of its deficiency on the peripheral nerve damage after reperfusion injury.

A complete reference list can be found online at www.expertconsult.com.

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Graft Thrombosis

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Based on a previous edition chapter by Bjoern D. Suckow and David H. Stone

INTRODUCTION	614
INTRAOPERATIVE GRAFT ASSESSMENT	614
Inspection and Palpation of Pulses	614
Ultrasonography	615
B-Mode Ultrasonography	615
Duplex Ultrasonography	615
Arteriography	616
Miscellaneous Techniques	617
Continuous-Wave Doppler	617
Angioscopy	617

<i>Intravascular Ultrasonography</i>	618
GRAFT THROMBOSIS: PATHOGENESIS	618
GRAFT THROMBOSIS: THERAPEUTIC APPROACH	619
Detection of Graft Thrombosis	619
Assessment of Neurologic Status	619
Anticoagulation	619
Etiologic Assessment	619
Early Graft Failure (0 to 30 Days)	620
Late Graft Failure (>30 Days)	622
CHAPTER ALGORITHM	623

INTRODUCTION

Postoperative graft thrombosis remains a significant clinical challenge in contemporary vascular surgical practice. Whether early or late, graft thrombosis continues to account for significant morbidity, limb loss, and mortality in patients requiring vascular intervention. Historically, at 1 year after infrageniculate bypass graft failure, more than 50% of patients will have undergone major amputations.^{1,2} Among the remaining patients, ischemic pain at rest or ulceration will have developed in 25%, and more than 15% will have died. Accordingly, underlying risk factors associated with graft failure continue to be the focus of vascular surgical outcome analyses and regional quality improvement groups alike.^{3–5}

The causes of graft thrombosis are multifactorial and involve patient demographics, risk factors, natural history, and comorbid conditions, as well as technical issues associated with arterial reconstruction. These risk factors and the technical aspects of reconstruction have an impact on graft patency (Table 48.1) from the initial operation through the entire follow-up period. Technical precision at initial reconstruction is imperative in order to achieve an optimal outcome. The technical result at the time of surgery forms a new baseline on which the progression of disease and development of intimal hyperplasia will occur. A superior technical result may minimize the impact of these factors, allowing greater patency and/or early detection of a failing graft, where an imperfect result may not. It has been estimated that technical errors account for 4% to 25% of early

failure after revascularization.^{6–8} Furthermore, optimal long-term graft durability remains, in part, predicated on lifetime surveillance, timely re-interventions, and vigilant risk factor modification.^{9–12} To facilitate intraoperative assessment of the technical adequacy of the reconstruction at the time of surgery, numerous diagnostic tools are available to the surgeon, and are reviewed here. This chapter will also focus on surgical revascularization, including autogenous and prosthetic conduits and factors associated with their failure. Understanding the etiology and clinical manifestations of graft thrombosis and current experience with available treatment options is crucial for achieving the best and most durable results after initial failure of revascularization.

INTRAOPERATIVE GRAFT ASSESSMENT

To ensure optimal patency after revascularization, it is imperative that the surgeon determines the technical adequacy of the reconstruction before leaving the operating room.

Inspection and Palpation of Pulses

The most convenient and readily available methods for graft assessment include inspection and palpation of pulses. These processes involve not only inspection of the graft itself for kinks, twists, and stenoses, but also examination of the distal

TABLE 48.1 Definitions of Graft Patency

Term	Definition
Primary patency	The bypass graft remains patent without any subsequent intervention.
Primary assisted patency	The bypass graft undergoes a pre-emptive intervention to maintain patency, such as endovascular balloon angioplasty or anastomotic revision; however, the graft has never thrombosed.
Secondary patency	The bypass graft has thrombosed and is patent again following lysis and/or thrombectomy. A concomitant endovascular intervention and/or open revision may also have been performed to aid with subsequent patency.

target vessel and of the revascularized tissue, where possible, comparing it to the pre-procedural status. Is the foot pink and perfused? Has capillary refill time been shortened? Is a pulse now palpable in the foot?

The process is facilitated by having the target organ, as much as possible, included in the sterile field and available to the surgeon for intraoperative examination. For example, for aortobifemoral or more distal bypasses, covering the steriley prepared feet with clear plastic bags permits rapid examination after completion of the bypass. However, inspection and palpation are subjective and thus susceptible to observer bias. Calcified arteries, secondary to long-standing diabetes, may not adequately transmit an improved pulse. The effects of anesthesia combined with concomitant chronic occlusion of runoff arteries may delay the appearance of adequate lower extremity reperfusion. Surgeons should be attuned to what may seem to be an overly strong graft or distal arterial pulse, often called a “water hammer pulse,” resulting from distal outflow obstruction.

Ultrasonography

Ultrasound technology provides multiple noninvasive modalities for the intraoperative and subsequent longitudinal assessment of arterial reconstructions.

B-Mode Ultrasonography

B-mode ultrasonography has been used intraoperatively to obtain anatomic images noninvasively, although it is more commonly used in conjunction with duplex ultrasonography. Initial experimental studies established that its ability to detect small defects in patients was comparable to that of arteriography.¹³ In an evaluation of arterial defects created in dogs, both arteriography and B-mode ultrasonography were nearly 100% specific in excluding arterial defects. However, ultrasonography has significantly greater sensitivity in detecting defects, 92% overall, than serial biplanar arteriography at 70% and portable arteriography at 50%. These techniques have comparable accuracy in detecting stenoses.

B-mode ultrasonography has utility in assessing lower extremity arterial reconstructions. Kresowik et al.¹⁴ reported

that in 106 patients, intraoperative B-mode ultrasonography detected defects in 20% of patients, and that half of these defects were deemed important enough to warrant correction. In follow-up, there were no early graft occlusions in the B-mode group, and no residual defects were discovered with duplex scanning follow-up in the postoperative period.

Intraoperative use of B-mode ultrasonography alone, however, is not without its problems.¹⁵ Because this modality does not evaluate blood flow, it cannot differentiate fresh thrombus from flowing blood, which has the same echogenicity. Compared with Doppler pencil probes, B-mode ultrasound probes are larger and cannot be sterilized, requiring a sterile covering containing a gel to maintain an appropriate acoustic interface. Significant operator experience is needed to obtain optimal images and make accurate interpretations.

Duplex Ultrasonography

With the addition of flow-measuring capability to B-mode ultrasonography, duplex scanning brings a more powerful tool to the operating room. Like B-mode ultrasound probes, duplex scanning probes are large, cannot be sterilized, and require considerable operator skill so that accurate velocity and imaging data can be obtained. Duplex color-flow technology provides continuous Doppler signals along the graft and artery at multiple points. Color imaging facilitates identification of areas of higher velocity.¹⁶

Duplex scanning provides an alternative mechanism for identifying defects in proximal arterial anastomoses in situations where placing a catheter for arteriography proximal to the proximal anastomosis is cumbersome or difficult.¹⁷ In addition, duplex scanning can identify low graft velocities that are only indirectly measured by arteriography and depend on the observations of the surgeon. Intraoperative experience with this imaging modality has shown greater sensitivity for detecting technical defects than other methods. Early results with intraoperative duplex scanning have demonstrated an association between these defects and suboptimal results in the postoperative period.^{18,19} A study by Rzucidlo et al.²⁰ reported intraoperative completion duplex scanning to be a useful tool after the completion of infrageniculate arterial reconstruction. Specifically, the authors documented that a 10-MHz, low-profile transducer could be used successfully to identify compromised grafts with a predilection for early failure. Moreover, it was determined that low end-diastolic velocity (EDV) was both associated with, and predictive of, early graft failure. Further, Scali et al.²¹ validated the utility of intraoperative completion duplex scanning following distal bypass, documenting that EDV measurements less than 5 cm/s predicted early graft failure (Fig. 48.1). Johnson et al.²² found that duplex use was associated with a 15% intraoperative revision rate that resulted in a significant reduction in early graft failure/revision. However, it is important to note that duplex ultrasound has some important drawbacks. It is challenging and sometimes not possible to assess newly placed polytetrafluoroethylene (PTFE) and polyester (Dacron, Hemashield) grafts because the graft walls contain air, which prevents penetration of the ultrasound waves. Furthermore, it can be difficult to assess the outflow in

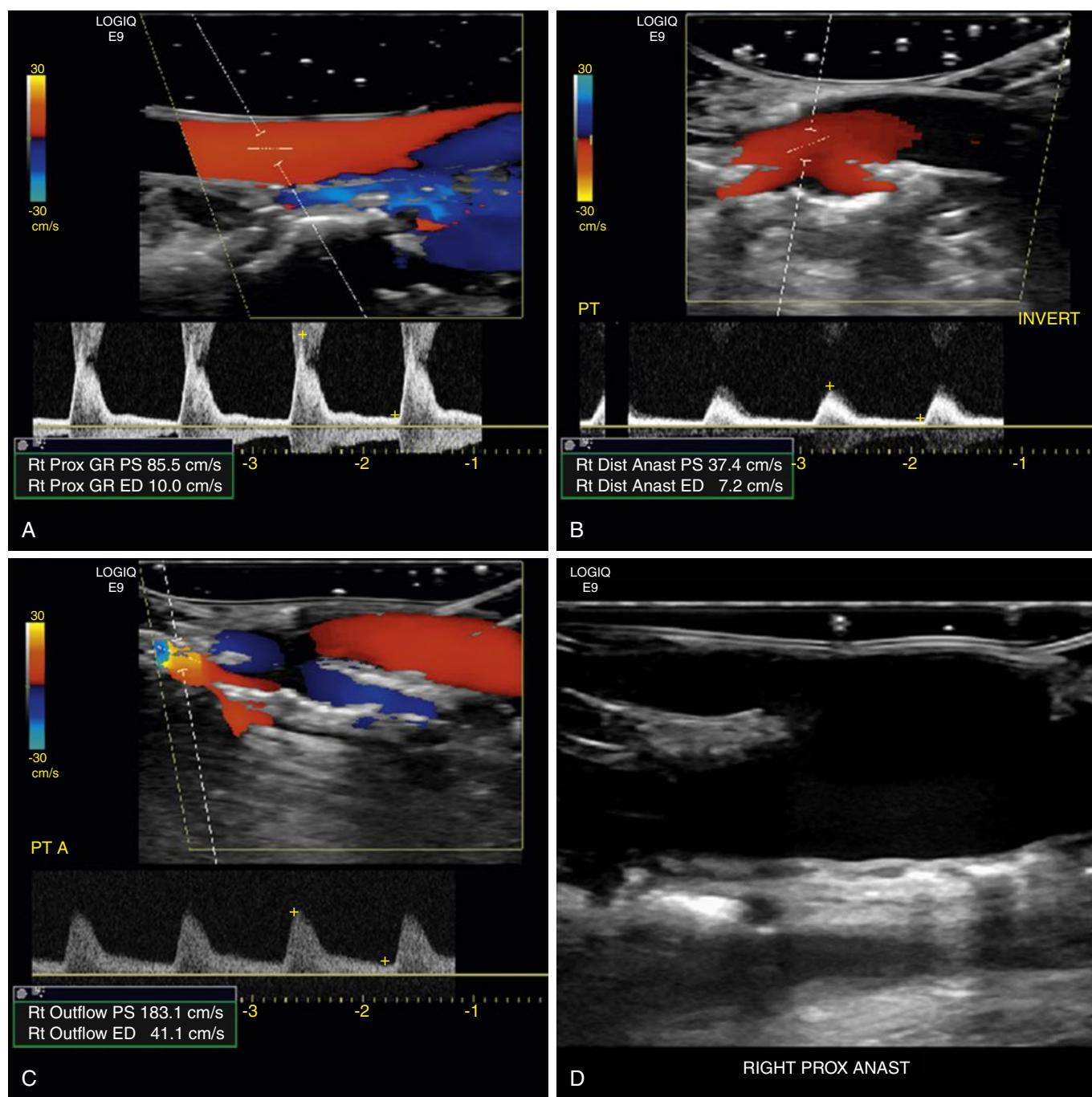


Figure 48.1 Intraoperative completion duplex ultrasound after a femoral to below-knee popliteal artery bypass graft with vein conduit. (A) The proximal part of the graft shows good diastolic flow as indicated by an end-diastolic (ED) velocity of 10 cm/s. (B) Patent distal anastomosis without stenosis as indicated by peak systolic (PS) velocity of 37.4 cm/s. (C) Antegrade blood flow in the native outflow artery with good diastolic flow as indicated by ED velocity of 41.4 cm/s. (D) No dissection flap, stenosis, or technical complication at the proximal anastomosis as seen on B-mode ultrasound.

the foot following bypass creation due to the presence of vasoconstriction or outflow disease.

Arteriography

Since its introduction, intraoperative completion arteriography has been the gold standard for anatomic evaluation of the technical adequacy of arterial reconstructions. One appealing

feature of arteriography is its ability to assess anatomic arterial outflow – the “runoff.” This is particularly important in the clinical context of preoperative studies that fail to reveal adequate target vessels in diffusely diseased vascular systems. Although completion arteriography is an invasive procedure associated with potential complications because of arterial puncture (intimal injury, dissection), injection (air embolism),

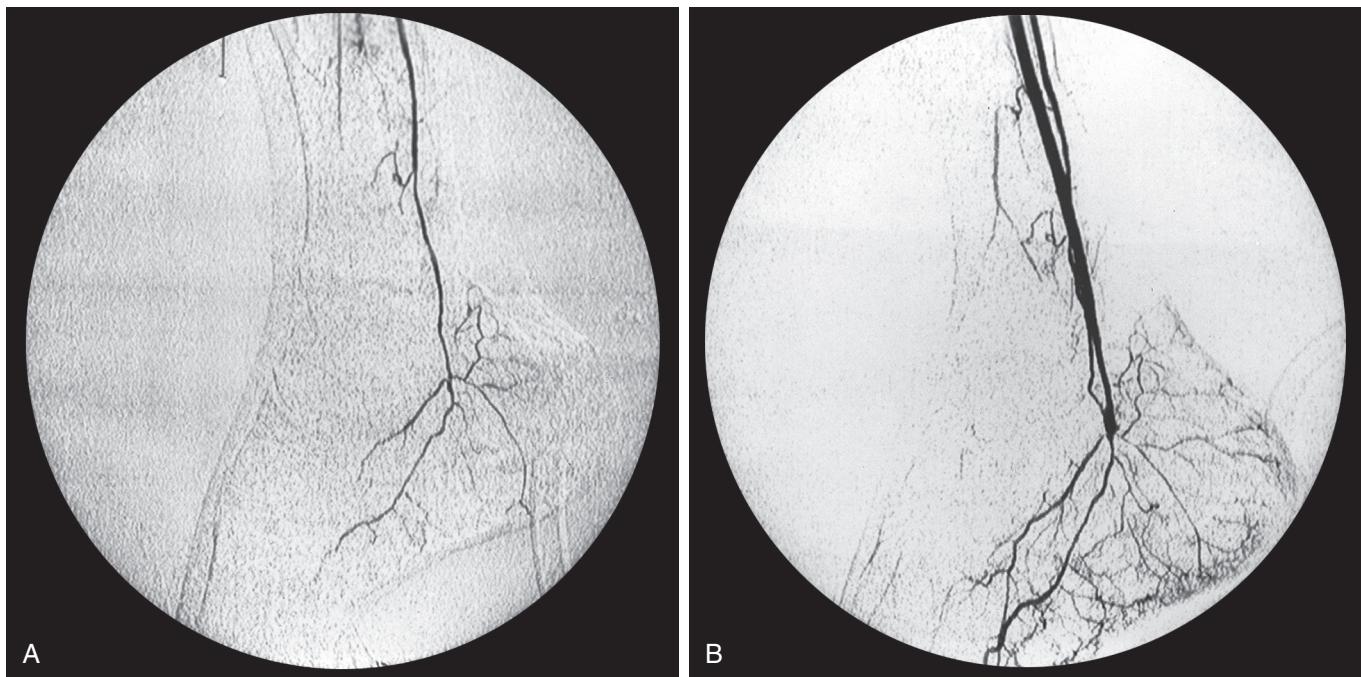


Figure 48.2 Intraoperative digital subtraction angiographic images of the plantar circulation performed (A) before and (B) after bypass.

use of radiographic contrast agents (renal failure, anaphylaxis), and radiation exposure, the actual observed complication rate has been negligible in large series.^{23,24} Arteriography has become our method of choice for intraoperative graft assessment because like most vascular surgeons we are comfortable performing this technique and at interpreting arteriographic images. Additionally, an increasing number of vascular surgeries are performed in operating rooms with fluoroscopic capability which makes it quick and easy to perform arteriography.

The technique varies according to individual application but generally involves insertion of an 18- to 20-gauge plastic angiocatheter or 4- to 5-Fr sheath into the arterial graft to allow subsequent injection of 10 to 30 mL of radiographic contrast agent. Temporary occlusion of arterial inflow maximizes the concentration of contrast agent without the need for excessively rapid injection. Digital subtraction angiography, rather than simple fluoroscopy with concomitant contrast injection, will then provide clearer images and allow for visualization of vessel patency and runoff (Fig. 48.2).

Indirect information obtained with angiography includes the observed flow rate (emptying) of the conduit which provides an estimate of conduit patency and outflow. When evaluating autogenous conduits, the proximal anastomosis and the entire conduit should be included in the evaluation. This allows for the detection of proximal anatomic defects as well as the presence of any intrinsic defects or twists within the conduit itself. In the setting of an *in situ* reconstruction, the presence and location of arteriovenous fistulas can be identified and treated. For prosthetic grafts, the graft itself may be punctured and the evaluation begins with the distal anastomosis. Care should be taken during injections to ensure that there are no air bubbles or overlying structures that may lead to false-positive interpretations. Recalling that angiography is a

two-dimensional modality this method can result in underestimation of the stenosis from a small defect, such as an intimal flap or platelet aggregate.²⁵ Contrast density may be reduced in a focal area suggesting such an occurrence and an oblique projection may more definitively reveal an underlying defect.

Miscellaneous Techniques

Continuous-Wave Doppler

The simple and inexpensive continuous-wave Doppler 8- to 10-MHz pencil probe is readily available for intraoperative use. It is frequently used to assess flow in the target or outflow vessel(s). Further, the probe can be passed along the graft and anastomoses, where localized increases in the audible sound frequency or audible turbulence could indicate a potential defect.

Use of the audible continuous-wave Doppler technique is subjective and operator dependent. Considerable experience is required for maximum accuracy and it is not highly sensitive.²⁶ Most vascular surgeons use this modality as an easy, available, and inexpensive screening device to guide their use of a more precise evaluation technique.

Angioscopy

Intraoperative angioscopy is another technique for evaluation of arterial reconstructions and thorough interrogation of autogenous conduit. As with duplex ultrasonography, experience is required to manipulate both the angioscope and the visual target to obtain adequate visualization.

Angioscopy has been most widely used for inspection of *in situ* saphenous vein grafts to ensure complete valve lysis,²⁷ to exclude unligated venous branches, and to assess the quality of the venous conduit (Fig. 48.3). It should be noted that

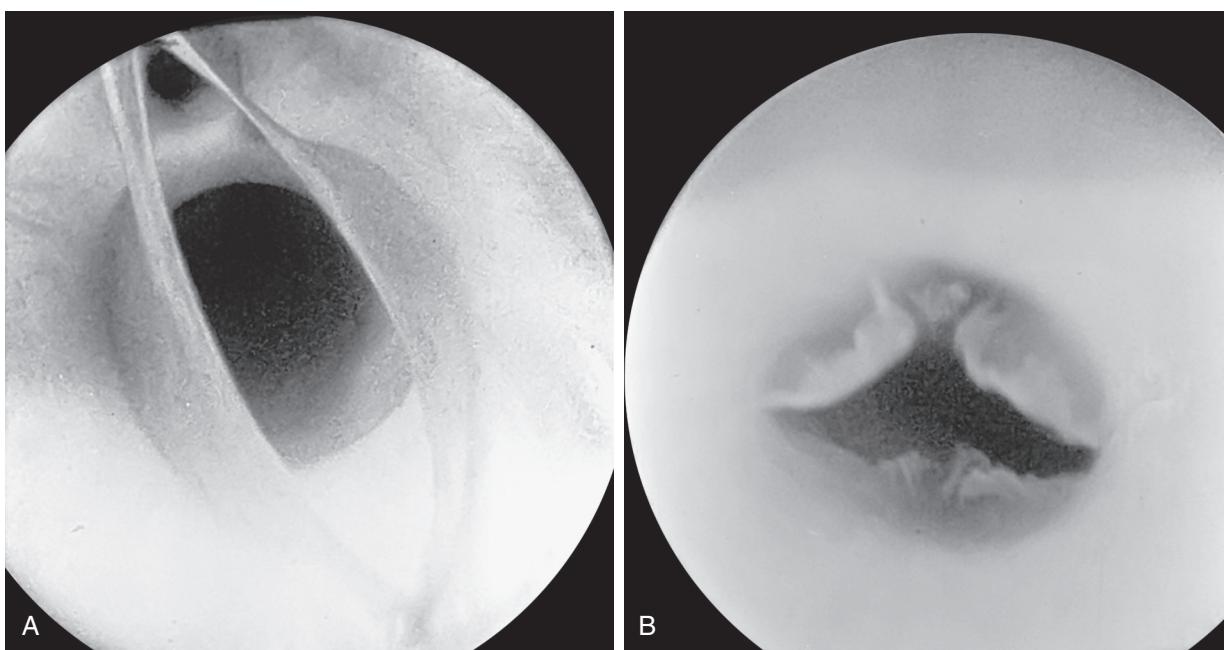


Figure 48.3 (A) Photograph of a valve via an angioscope before lysis. (B) Photograph of an angioscopic image of a valve after lysis. (B, From McCaughan JJ Jr, Walsh DB, Edgcomb LP, et al. In vitro observations of greater saphenous vein valves during pulsatile and nonpulsatile flow and following lysis. *J Vasc Surg*. 1984;1:356.)

experimental studies have documented that mild intimal injury may occur with angioscopy. However, such injury occurs only after multiple repeated passages of larger diameter scopes.²⁸ The long-term effects of this mild trauma have not been firmly established.^{29,30}

Intravascular Ultrasonography

More frequently in contemporary practice, intravascular ultrasound (IVUS) has become a useful intraoperative imaging adjunct. Both IVUS and angioscopy were found to be 100% accurate in detecting 2-mm intimal flaps in canine femoral arteries, compared with only 60% accuracy for single-plane arteriography.³¹ Although IVUS appears to be useful in endovascular procedures,³² it is unclear whether IVUS will provide information that is different and useful enough to justify its use in evaluating the technical adequacy of vascular surgical reconstructions.

GRAFT THROMBOSIS: PATHOGENESIS

Despite meticulous attention to preoperative planning and to technical perfection in the operating room, revascularizations may be unsuccessful for a variety of reasons. Depending on the type of arterial reconstruction, between 0.3% and 10% fail in the early postoperative period.^{1,4,33} Early graft thrombosis has significant prognostic implications, in that a failed reconstruction is associated with poor clinical outcomes, particularly when performed for limb salvage indications.^{34–36} Several studies have identified a variety of factors potentially contributing to graft failure, including patient demographics, risk factors, comorbid diseases, conduit characteristics, anesthesia type, adjuvant medical therapy, and technical precision.^{4,37–41} A study from the Washington Hospital Center and Georgetown

University Medical Center prospectively collected and analyzed the National Surgical Quality Improvement Program (NSQIP) database from 1995 to 2003 in an attempt to elucidate risk factors predictive of graft failure in patients who underwent infringuinal arterial bypass. Multivariate logistic regression revealed that younger age (<60 years), African American race, and crural target vessel were associated with graft failure.⁴ Another more recent study by Soma et al.⁴² confirmed the above findings and also identified female sex, obesity, thrombocytosis, increased international normalized ratio, femoral-to-tibial bypass, prosthetic graft, and emergent operation as additional risk factors for early graft failure. Furthermore, Giswold et al.¹ documented that dialysis dependency, a known hypercoagulable state, ongoing smoking, and failure to undergo routine graft duplex surveillance were all independently associated with reversed vein graft occlusion. Further, Oresanya et al. added that a small vein graft diameter (<3 mm) and the nonadherence to ultrasound surveillance are independently associated with graft failure.⁴³ In addition, Nolan et al. indicate that bypass grafts performed in limbs where a previous endovascular intervention was performed have a significantly higher failure rate than grafts performed in limbs without a prior endovascular intervention (28% occlusion rate versus 18% occlusion rate).⁴⁴

The role of hypercoagulability as a cause of graft failure has become increasingly recognized in contemporary practice. As the population ages, it has been hypothesized that the number of arterial reconstructions will increase.^{1,34,45} This, coupled with the introduction and evolution of newer technologies, will lead to an increasing number of interventions that a typical patient will undergo, thereby compounding the impact of hypercoagulability in light of the inherent multiple previous exposures to heparin.^{46–48}

Long-term follow-up has demonstrated that nearly 50% of vascular reconstructions are subject to some degree of restenosis or eventual occlusion,^{33,49} and thus has confirmed the efficacy of aggressive graft surveillance and subsequent endovascular or conventional surgical revision in an attempt to identify and prospectively repair deteriorating grafts and prevent graft occlusion.^{36,49–52}

When thrombosis does occur, therapeutic alternatives range from expectant supportive care to thrombectomy, thrombolysis, or placement of an entirely new arterial reconstruction. Optimal results in these most difficult circumstances require rapid decisions by the surgeon regarding the etiology of the graft failure and/or thrombosis, selection of either surgical or endovascular repair, timing of re-intervention, and assessment and modification of complex patient risk factors. This discussion summarizes therapeutic guidelines for the most frequently encountered scenarios after thrombosis of an arterial reconstruction.⁵³

GRAFT THROMBOSIS: THERAPEUTIC APPROACH

Detection of Graft Thrombosis

It is incumbent on the clinician to document graft thrombosis in a timely fashion. This may be as simple as noting the absence of a previously palpable pulse combined with dramatic progression or return of the patient's ischemic symptoms. In less obvious circumstances, noninvasive testing to measure the ankle–brachial index and the use of duplex ultrasonography to determine patency and the location of the occlusion or restenosis may obviate the need for administration of contrast material. This is particularly germane in light of the fact that the patient will probably require further contrast as part of the definitive revision and/or reconstruction.

Assessment of Neurologic Status

A primary determinant of the necessity for and urgency of aggressive intervention is the patient's neurologic status at initial evaluation. As the level of neurologic dysfunction increases from dysesthesia to paralysis, the impetus for rapid resolution of the situation grows. Consequently, the time available for lengthy diagnostic or therapeutic measures outside the operating room decreases correspondingly. Considerable clinical judgment is required in these cases because delay in treatment may precipitate irreversible tissue injury and culminate in untoward outcomes, including limb loss or death. A standardized approach to and reporting of the acutely ischemic limb was published by Rutherford in 1997.⁵⁴ The Rutherford criteria of acute limb ischemia based on sensory function, motor function, and presence or absence of ankle Doppler signals continues to be a useful measure of the degree of acute ischemia. This approach will aid the clinician in determining the rapidity with which revascularization is necessary or perhaps even contraindicated. A nonviable limb, Rutherford category III, would preclude an attempt at revascularization, while a Rutherford category IIb limb should prompt urgent revascularization.

If there is no neurologic compromise and the degree of tissue ischemia appears minimal, such as in Rutherford category IIa or category I, diagnostic or alternative therapeutic maneuvers, including thrombolysis, can be contemplated, although not in the early postoperative period (see Ch. 43, Thrombolytic Agents). This is predicated on recognition of the delayed therapeutic efficacy associated with thrombolytic therapy. Nevertheless, adequate clinical outcomes with thrombolytic therapy can be anticipated when applied in select clinical circumstances.^{55–57} However, it should be emphasized that secondary patency after treatment of infrainguinal graft thrombosis is generally poor. If the initial reconstruction was performed for ongoing tissue loss, and the ulcer or amputation has subsequently healed, urgent revascularization may not be required. Likewise, graft failure in the setting of recurrent claudication may not warrant urgent reintervention, particularly if a patient has extensive medical comorbidities.

Anticoagulation

Once the diagnosis of graft thrombosis has been confirmed, immediate anticoagulation becomes imperative to minimize or halt thrombus propagation. A short interval to permit blood collection for determination of hypercoagulability is permissible. If regional anesthesia is preferred for a surgical attempt at graft salvage, systemic anticoagulation can be delayed until anesthesia is achieved. If immediate surgery is not required or regional anesthesia is contraindicated, either systemic heparinization or anticoagulation with an alternative agent, when appropriate, should be instituted to inhibit ongoing thrombosis.

Etiologic Assessment

Several factors that may contribute to any graft failure should be investigated. If not previously established, the patient's coagulation status should be determined. As noted earlier, graft thrombosis at any time after placement can be the consequence of a previously unrecognized hypercoagulable state (see Ch. 40, Disorders of Coagulation: Hypercoagulable States).^{47,58–60} If a hypercoagulable state is suspected a blood specimen should be collected and sent immediately (before anticoagulation) for measurement of standard coagulation parameters, including platelet count, functional activated protein C resistance, anticardiolipin antibodies, antithrombin III, and protein S when feasible. Previous exposure to heparin, with consequent heparin-associated antibodies causing platelet aggregation, should be investigated and routinely considered in current practice scenarios because previous exposure to heparin is increasingly common, perhaps secondary to the advent and application of less invasive percutaneous interventions.^{47,61} Failure to recognize this insidious condition can lead to poor clinical outcomes and recurrent graft thrombosis.^{58,62} As the incidence of heparin-induced thrombocytopenia becomes more prevalent, so too will the untoward effects of administration of unfractionated and low-molecular-weight heparin.⁶² Alternatively, less likely causes of hypercoagulable complications leading to thrombosis include increased blood viscosity

from dehydration, polycythemia, or sepsis, which can easily be diagnosed by physical examination and routine hematologic screening. A multivariate analysis from NSQIP implicated thrombocytosis as being independently associated with early graft failure, although this has not been widely studied in other analyses.³ Acute or chronic cardiac decompensation is an uncommon but real cause of failure of arterial revascularization; these conditions can be rapidly detected at initial patient evaluation with electrocardiography or echocardiography, as indicated. Rapid cardiac assessment is also critical in assessing the risk associated with various possible therapeutic options.

The first element fundamental to achieving successful treatment of a failed revascularization is accurate determination of the cause of the thrombosis. As noted previously, the incidence of technical errors as a cause of early graft failure has significantly decreased over the last 40 years. Technical errors now account for 20% or less of thromboses in arterial reconstructions in the early postoperative period, despite the historical supposition to the contrary. Other probable causes include inherent thrombogenicity of the graft conduit, underappreciated or unrecognized patient-related hypercoagulable states, and poor target artery selection with disadvantaged runoff.

One analysis of roughly 2500 patients from the Vascular Study Group of New England, a regional quality improvement initiative, revealed several predictors of both early and late graft occlusion. Specifically, both a below-knee target and a tarsal distal target were predictive of diminished graft patency, as was a secondary reconstruction or “redo” revascularization in the early postoperative period. Analysis also determined that diabetes, preoperative tissue loss, greater body mass index ($>35 \text{ kg/m}^2$), and reconstructions requiring early revision (primary-assisted patency) were predictive of diminished long-term graft patency.⁶³ Similarly, a review of high-risk bypass grafts performed for critical limb ischemia by Rzucidlo et al.²⁰ found the rate of graft failure within 12 months to be 44%. Noted risk factors included compromised distal arteries that previously required thrombectomy, single-vessel outflow, inability to pass a 1-mm dilator into the outflow vessel, or disadvantaged vein conduits that required interventions such as venovenostomy, vein patch angioplasty, or prosthetic interposition.

A useful construct for determining the etiology of an unsuccessful arterial revascularization includes examination of each of the elements required for effective durable graft patency. The five elements critical for sustained function of an arterial reconstruction are *inflow*, *outflow*, *conduit*, *operative technique*, and *coagulation profile*.

For any revascularization to function, blood pressure, and blood flow at the origin of the reconstruction must be the same as the systemic parameters. Compromised inflow noted by a gradient between the proximal reconstruction and central systemic arterial pressure demonstrates the existence of a significant proximal arterial stenosis. If uncorrected, suboptimal clinical outcomes and graft durability can be expected.

The quality of outflow for a revascularization can be extremely difficult to characterize. For example, in the setting of lower extremity revascularization, only a few small vessels may constitute the outflow runoff, which at arteriography appears

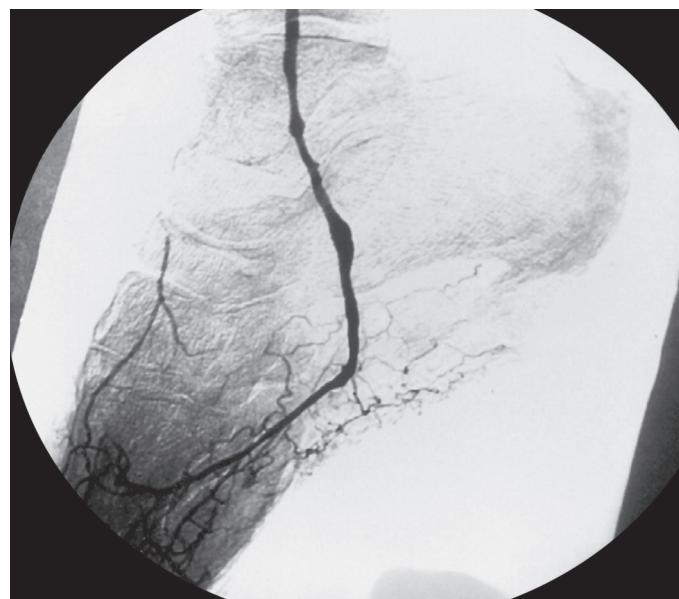


Figure 48.4 Intraoperative completion arteriogram demonstrating sparse runoff from a lateral plantar artery.

too sparse to support durable graft function. In certain cases a distal runoff vessel may appear robust enough to support a distal bypass as is the case for this lateral plantar artery (Fig. 48.4). Despite attempts to correlate the radiographic features depicted on angiograms with impending graft thrombosis or failure, no consistent angiographic criteria have been determined to be reliable predictors of graft patency. However, several large-cohort reviews have identified poor runoff as an independent risk factor for graft thrombosis.

When considering both the timing and the etiology of failed arterial reconstructions, two temporal categories should be taken into account as they dictate initial approach: early (within 30 days of placement) and late (after 30 days) (Table 48.2). This discussion focuses primarily on outcomes of infrainguinal revascularization, which forms the largest cohort of failed revascularizations.

Early Graft Failure (0 to 30 Days)

Despite improvement in infrainguinal vein graft revascularization techniques, 5% to 10% of grafts fail within 30 days of placement.³³ The time elapsed from initial revascularization is the single most important characteristic aiding in determination of the cause of the graft failure (Fig. 48.5). Early (<30 days) thrombosis of vascular reconstructions has historically been attributed to technical error.⁶ In a review of the Dartmouth-Hitchcock experience, it was found that technical errors accounted for roughly 25% of early graft failures.⁷ Since that time, the number of graft failures referable to technical error has declined sharply (10%).⁵³ This improvement can be directly attributed to the routine use of angioscopy, duplex ultrasound scanning, and angiography to confirm the technical adequacy of the arterial reconstruction. Such confirmation also permits a prospective, qualitative determination of the likelihood that graft failure will occur, and a recognition that it is most likely related to the conduit or the quality of the runoff

TABLE 48.2

Classification of Graft Failure by Time Interval with Associated Causes and Treatments

Time	Etiology	Treatment
Early/mid-term failure	Technical	Thrombectomy
	Graft thrombogenicity	Thrombolysis
	Low flow	Patch angioplasty
	Poor runoff	
Late failure	Graft abnormality	Thrombolysis
	Metachronous disease	PTA
		Patch angioplasty
		Interposition graft

PTA, percutaneous transluminal angioplasty.

bed. In addition, thorough graft interrogation greatly simplifies further therapeutic clinical decision-making. For example, if a failed graft was constructed with the only available autogenous vein conduit to the only possible target runoff vessel, and it showed no evidence of an anastomotic or an intrinsic conduit problem at the time of placement, early amputation might represent the optimal strategy to achieve the best possible outcome. In other words, if such a patient undergoes further attempts at thrombectomy, revision of the anastomosis, replacement of the conduit, or substitution of the runoff, they are only likely to sustain increased morbidity, mortality, and expense, with little improvement in the chance for limb salvage.³⁴

After diagnosis of a graft that failed early in the postoperative period, the surgeon must first determine whether to proceed with attempted salvage of the initial bypass graft. Commonly used options include either surgical thrombectomy, percutaneous mechanical thrombectomy or thrombolysis. The results of all techniques remain discouraging in the early postoperative time period, irrespective of the conduit used or the procedure performed. Furthermore, thrombolysis places the patient at significant bleeding risk, especially at recent surgical sites. A meta-analysis of three randomized studies and 14 review papers on thrombolysis for acute limb ischemia placed the risk of major hemorrhage associated with thrombolysis at nearly threefold higher than nonlytic therapy (OR 2.85).⁶⁴ A separate Cochrane review of thrombolysis for acute limb ischemia similarly identified a 200% increase in major bleeding risk.⁶⁵ The risk of major bleeding therefore could preclude a significant patient subset with graft thrombosis from undergoing thrombolysis.

After thrombolysis is attempted in the early postoperative period, the extended patency of thrombosed vein grafts ranges between 15% and 20% at 1 year.^{57,66,67} In one series, 3% of patients died, 14% experienced bleeding complications requiring transfusion, and 13% developed thromboembolic complications. Despite these associated complications, 75% of the treated limbs had been salvaged at 1 year. Results with thrombolysis of prosthetic grafts are slightly better, although this difference

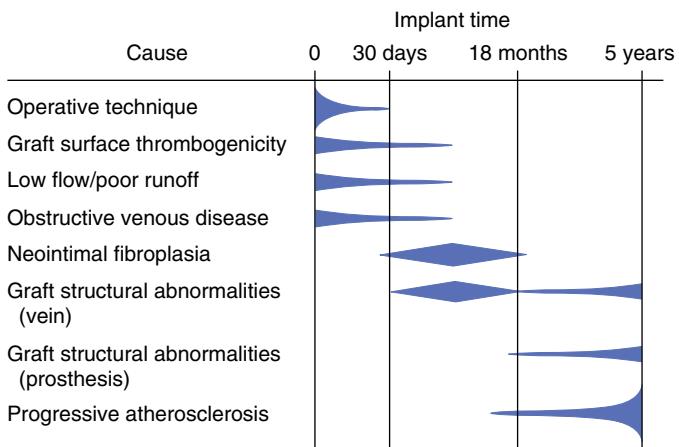


Figure 48.5 Factors Contributing to Graft Occlusion with Time. (Modified from Rutherford RB. The prevention and management of graft thrombosis. In Kempczinski RF, ed. *The Ischemic Leg*, Chicago, IL: Year Book Medical; 1985.)

is probably related to the better runoff than usually exists when prosthetic graft material is used as the conduit for the initial bypass procedure.⁶⁸ Vein graft longevity after thrombolytic intervention has been documented to correlate with the time interval since the vein graft was placed.⁶⁹ Specifically, a shorter interval to graft failure will have a diminished likelihood for success with thrombolytic therapy, particularly in patients with diabetes. Review of a single institution experience found that no patient with diabetes and a recently placed graft achieved reasonable secondary graft patency with thrombolysis.⁶⁷ Of patients treated successfully with lytic therapy, 44% ultimately required early amputation, whereas in patients in whom thrombolysis failed, the amputation rate approached 69%.

Like lytic therapy, the results of surgical thrombectomy for early graft failure are also relatively disappointing, even with an adjunctive procedure such as patch angioplasty of the responsible lesion or lesions. Among 36 vein bypasses in which patency was reestablished within 1 month after surgery via surgical thrombectomy, graft stenosis was noted in as many as 39% of arterial reconstructions. Such stenosis is possibly due to rapid degeneration of normal cellular function in the thrombosed vein wall.⁷⁰ Late bypass revisions, performed in 35% of grafts, did little to improve 1-year patency rates, which approached 38%.⁷¹ Robinson et al.³⁴ reported a cumulative secondary patency rate of 47% at 1 year. In this series, 26% of the patients required amputation within 1 month of graft thrombectomy, and 41% required amputation by 1 year. The results of surgical thrombectomy were significantly improved if technical problems (e.g., a twist in the graft or a retained valve cusp in an *in situ* saphenous vein bypass graft) were identified at exploration.

It should be reemphasized, however, that the incidence of graft failure referable to technical error has substantially decreased.³⁴ It is our practice to perform immediate reexploration in any patient with perioperative graft failure, irrespective of the conduit, when at initial surgery all components of the revascularization were judged technically optimal and in no way disadvantaged. In this setting, thrombolysis poses an additional risk of bleeding, delayed efficacy, and overall poor long-term results. Therefore, in such patients, thrombectomy,

anticoagulation, and repair of any underlying potential technical problems yield superior results.^{72–75} It is important to note, however, that in as many as 50% of patients who undergo reexploration for early graft failure, no underlying cause of thrombosis is found.⁶

Percutaneous mechanical thrombectomy has emerged as an attractive alternative to surgical thrombectomy and thrombolysis owing to its minimally invasive nature and also because it obviates the need for lytic agents in many circumstances. Currently available mechanical thrombectomy devices can be broadly characterized into: (1) suction thrombectomy catheters (Penumbra/Indigo Systems (Penumbra Inc)); (2) recirculation thrombectomy devices that break down clot via rheolytic fluid dynamics (Angiojet Thrombectomy system, Boston Scientific); (3) nonrecirculation thrombectomy devices that macerate thrombus; and (4) energy-assisted devices such as the EkoSonic endovascular system (Boston Scientific) that use ultrasound to lyse thrombus or enhance the effects of pharmacologic agents.^{76,77} Additionally, certain devices such as the Angiojet thrombectomy system (Boston Scientific) allow for limited and targeted tPA infusion when thrombolytics are deemed necessary. This is especially valuable in patients deemed high risk for bleeding complications. Finally, pre- and post-intervention angiography is typically performed with this technique, which aids in the identification of technical errors or other pathology for more targeted surgical or endovascular intervention. Traditionally a common limitation of percutaneous mechanical thrombectomy has been their inability to completely clear thrombus in large-diameter vessels. Newer devices appear to be more effective than previous iterations in this regard. However, more extensive studies are required to support this.

If attempts to salvage a thrombosed infrainguinal graft remain unsuccessful in the early postoperative period, two options remain. One management strategy includes expectant therapy and anticoagulation. Frequently, amputation will ensue, although limb loss is not inevitable.^{75,78} An alternative strategy includes performing a new bypass procedure, ideally with the best available autogenous vein, assuming that there is adequate residual conduit length and an additional good quality target vessel. Although seemingly difficult, this aggressive posture often leads to improved results.⁷⁹ In the absence of a suitable vein conduit, alternative options including prosthetic grafts or cadaveric vein can be used, though the results have not been particularly durable.⁸⁰ Frequently, partial preservation of a pre-existing graft is possible with thrombectomy and extension to a new distal target. It has been our practice to be very aggressive in re-bypassing patients with imminent limb-threatening lower extremity ischemia who have failed salvage attempts. A review of our experience at Montefiore Medical Center revealed the likelihood of success of repetitive limb revascularization to be unrelated to the number of previous failures. Additionally, we found that the three-year limb salvage rate was over 50% in patients who otherwise would have required amputation.⁸¹

Late Graft Failure (>30 Days)

Many of the aforementioned diagnostic and therapeutic decisions remain germane in the setting of delayed or late graft

failure. There are, however, several distinctions. First, technical errors no longer constitute a significant cause of graft pathology. Second, thrombolytic therapy offers greater therapeutic utility in this time interval. Third, a greater magnitude of technical difficulty can be anticipated in the surgical dissection of previously operated vessels.

The time interval since arterial reconstruction can act as a positive predictor of the successful application of thrombolytic therapy. Specifically, the longer a graft has been in place, the greater the likelihood that thrombolytic therapy will confer graft patency. Two factors have been noted in the Dartmouth experience to be critical in predicting success after lytic therapy: graft age (since time of placement) of approximately 1 year or older, and the absence of diabetes. It was noted that although thrombolysis was successful in 15 failed grafts in patients with diabetes, only 1 graft was patent at 1 year. Conversely, in non-diabetic patients with at least 12 months of documented graft patency before thrombosis, 44% of patients achieved documented graft patency at 2 years.

After restoration of graft patency, it has been well-documented that further endovascular or surgical therapy may be required in up to 85% of cases to achieve sustained patency. Available therapeutic options in this setting include: (1) balloon angioplasty of an intragraft or juxta-anastomotic stenoses; (2) open surgical vein patch angioplasty; and (3) interposition bypass reconstruction. Although the results of such techniques when applied to failed grafts successfully treated with lytic therapy (secondary patency) are not comparable to the documented outcomes observed when applied to maintain the patency of threatened grafts (assisted primary patency), the “threatened” group constitutes a larger cohort and provides a significant body of data from which the surgeon may guide clinical decision making.

Endovascular therapy has become an important adjunct in the maintenance and restoration of graft patency following lytic therapy. Several groups have reported patency rates from 40% to 86% following angioplasty or vein patch angioplasty for failing/threatened bypass grafts.^{82,83} In a patient with a failed prosthetic bypass graft secondary to progressive advanced atherosclerotic disease compromising outflow circulation, percutaneous treatment with angioplasty or other endovascular adjuncts can help prolong graft patency and obviate the need for surgical intervention.^{84,85}

Selective application of patch angioplasty versus interposition grafting to address a vein graft lesion noted after successful thrombolysis should best be decided on the basis of lesion location and appearance, availability of adequate autogenous conduit, and surgeon preference. Review of both techniques demonstrates that similar results and outcomes can be expected.⁸⁶ Although some suggest superior outcomes with a vein interposition graft to treat an intimal hyperplastic lesion, the requisite additional anastomoses carry their own potential associated complications.

The optimal autogenous vein conduit for replacement of a short segment of vein graft is ideally derived from either the remaining ipsilateral saphenous vein or the lesser saphenous vein. Insertion of a segment of contralateral great

saphenous or arm vein as a short interposition graft segment should be avoided to preserve these intact longer conduits for alternative or metachronous uses. In patients who have older grafts with acquired diffuse degeneration or in patients with diabetes whose grafts have failed in less than 1 year after implantation, thrombolysis is unlikely to confer any significant secondary graft patency. Rather, a repeat bypass is more likely to offer successful long-term patency. This supposition is predicated, however, on the availability of sufficient quality distal target vessels and adequate autogenous conduit. When these are available, there does appear to be an enhanced sustained benefit associated with repeat bypass when applicable.

The choice of conduit constitutes yet another example of the associated clinical decision-making complexity when confronted with a failed graft. Historically, the contralateral great saphenous vein has been thought to be the preferred source of conduit for bypass in the setting of an inadequate ipsilateral great saphenous vein because of either disease or previous use. Appropriate concern that the donor extremity will potentially require future bypass or that the saphenous vein might better be used for coronary artery bypass has traditionally been outweighed by the more immediate need and clinical gravity. However, some have questioned this conduit selection algorithm owing to high re-intervention rates in some series (nearly 6% per year) with the majority of these (83%) being contralateral infraginguinal bypass.⁸⁷

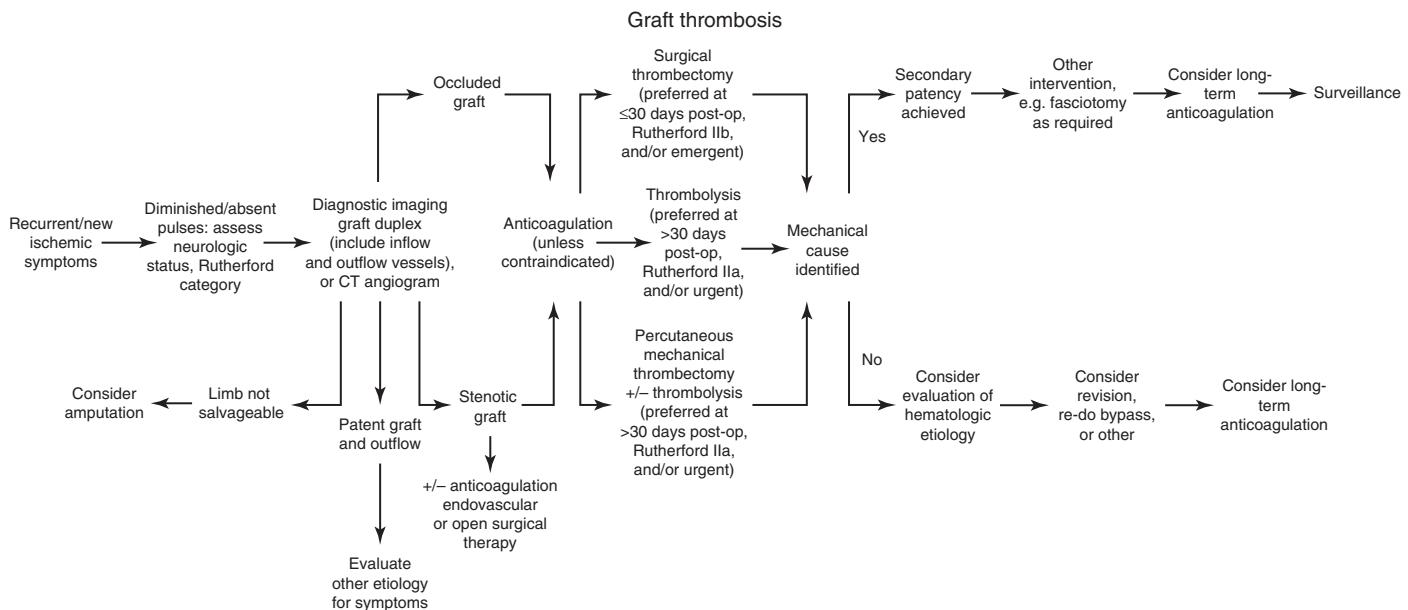
Factors predictive of the need for future intervention at the time of initial ipsilateral revascularization included younger age, diabetes, coronary artery disease, and diminished contralateral ankle–brachial index.

In light of these findings, selection of the most appropriate bypass conduit, when the ipsilateral great saphenous vein is not

available, remains a complex decision confronting the vascular surgeon. Arm veins, when deemed acceptable on preoperative duplex evaluation, remain an appropriate alternative conduit for graft revision or secondary bypass. Although the need for graft revision remains greater in reconstructions in which an arm vein was used as the conduit, documented assisted primary patency rates approach 72% over 5 years.⁸⁸ Although alternative vein grafts spliced together from the lesser saphenous vein and the remaining ipsilateral saphenous vein have been documented to have equivalent patency to that of an arm vein, the associated added morbidity of distal incisions in an ischemic, previously operated limb should not be underestimated. Use of an arm vein conduit may also minimize the number of venostomies required in the scenario of small segments of a viable lower extremity conduit. Regular use of the profunda femoris artery and endarterectomy of the superficial femoral artery to lessen the requisite conduit length for bypass are important surgical adjuncts that should be incorporated into treatment paradigms.

Although some advocate repeat infragenicular bypass with cadaveric vein or prosthetic conduit with or without a distal vein cuff or associated arteriovenous fistula, these options are generally reserved for limb threat in the absence of other therapeutic alternatives.^{89–92} In a comparative study of alternative graft conduits, Faries et al.^{93,94} documented that autogenous arm vein grafts demonstrated better patency than prosthetic conduit when applied to below-knee popliteal and tibial configurations. It is our continued preference to use autogenous vein when available and prosthetic grafts as a reasonable alternative to primary amputation, with cadaveric conduits reserved for extreme clinical circumstances in the setting of infection/tissue loss where less expensive prosthetic conduit might be at risk to become infected.

CHAPTER ALGORITHM



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This study is a National Surgical Quality Improvement Program analysis of a large cohort of patients that identifies predictors associated with early graft failure.

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A complete reference list can be found online at www.expertconsult.com.

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Graft Infection

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INTRODUCTION	625
INCIDENCE	626
PATHOGENESIS	626
Cellular and Biomolecular Events	626
Clinical Sources of Infection	627
<i>Perioperative Contamination</i>	627
<i>Bacteremia</i>	627
<i>Mechanical Erosion</i>	627
<i>Involvement by a Contiguous Infectious Process</i>	627
<i>Impaired Host Defenses</i>	628
Bacteriology	628
Prevention Principles	628
<i>Topical Antibiotics</i>	629
<i>Prophylactic Antibiotics</i>	629
DIAGNOSIS	629
Clinical Manifestations	630
Imaging Studies	630
<i>Contrast-Enhanced Computed Tomography and Computed Tomographic Angiography</i>	630
<i>Ultrasonography</i>	631
<i>Magnetic Resonance Imaging</i>	631
<i>Functional White Blood Cell Scanning</i>	631

<i>Endoscopy</i>	631
<i>Computed Tomography – Guided Aspiration Versus Operative Findings</i>	631
Culture Techniques	631
SURGICAL TREATMENT AND OUTCOMES	631
Treatment Considerations	631
Graft Preservation	632
Graft Excision And Extra-Anatomic Bypass	633
<i>Need for Revascularization</i>	633
<i>Graft Excision</i>	633
<i>Timing of Limb Revascularization</i>	634
In Situ Graft Replacement	634
<i>Autologous Graft Replacement</i>	634
<i>Neo-Aortoiliac System Reconstruction</i>	635
<i>Antibiotic-Treated Prosthetic Grafts</i>	636
<i>Cryopreserved Arterial Allografts</i>	636
Treatment Adjuncts	637
<i>Antimicrobial Agents</i>	637
<i>Antibiotic-Loaded Beads</i>	637
<i>Local Tissue Flap Coverage</i>	637
Endograft Device Infection	638
CHAPTER ALGORITHM	639

INTRODUCTION

The incidence of infection involving vascular prostheses is relatively low because of routine antibiotic prophylaxis before surgical procedures, refinements in the sterilization and packaging of devices, and careful adherence to aseptic procedural and surgical technique. When infection does occur, detection and definitive therapy of the vascular prosthesis are often delayed, with potentially catastrophic consequences. If it is not recognized or treated promptly, implant failure will occur as a result of sepsis, vessel disruption and hemorrhage, or thrombosis with end-organ ischemia.^{1–6} The clinical manifestations of prosthetic vascular infection vary depending on the anatomic location and the virulence of the pathogen.^{1,3,5,7–9} In general, surgical therapy is always required, often coupled with excision of the

prosthesis, because antibiotics alone are insufficient to eradicate an established infectious process. An appropriate treatment plan is influenced by the clinical findings, anatomic location, time since initial implantation, type of graft/device material, extent of infection, virulence of infecting organism, and the patient's underlying comorbid conditions.

Keys to a successful outcome include accurately identifying the infecting organism and the extent of the graft infection; administration of culture-specific antibiotic therapy; well-planned surgical intervention(s) to preserve, excise, or replace the infected graft; sterilization of the local perigraft tissues; and maintenance of adequate distal organ/tissue perfusion. Improved results have been reported in the past 30 years after both graft excision coupled with extra-anatomic bypass and *in situ* replacement procedures.^{10–18} Because most patients

TABLE 49.1

Incidence of Prosthetic Graft and Endovascular Device Infection Relative to the Implant Site

Infection	Incidence (%)
Graft Implant Site	
Descending thoracic aorta/thoracoabdominal	0.5–1.9
Aortoiliac	0.2–1.3
Aortofemoral	0.5–3
Femorofemoral	1.3–3.6
Axillofemoral	5–8
Femoropopliteal	0.9–4.6
Femorotibial	2–3.4
Carotid patch	0.25–0.5
Carotid–subclavian	0.5–1.2
Axillo–axillary	1–4
Endovascular Device	
Aortic endograft	0.1–1.2
Peripheral stent	<0.1

with late manifestations have a low-virulence graft infection, *in situ* replacement therapy with autogenous venous conduits, cryopreserved allografts, or antibiotic-impregnated prostheses to replace the infected grafts has evolved to become a preferred treatment strategy.^{10,12,13,18–26}

INCIDENCE

The reported incidence of infection involving a vascular prosthesis varies from 0.2% to 5% of open operations and is influenced by the implant site, indication for the intervention, underlying disease, and host defense mechanisms (Table 49.1).^{1,4–6,8,25,27–34} Graft infection occurs much less frequently than wound infection, with the incidence of early (<30-day) graft infection being in the range of 1% to 2%. Infection is more likely to involve prosthetic grafts implanted during an emergency procedure, when the prosthesis is anastomosed to the femoral artery or placed in a subcutaneous tunnel. In a Canadian prospective multicenter trial of non-ruptured AAA open repair, the incidence of graft infection was 0.2%,²³ similar to that reported after endovascular aneurysm repair (EVAR).^{31,35–37} Infection can also develop after deployment of a bare stent, but the incidence appears to be extremely low (<0.1%) (Box 49.1).

PATHOGENESIS

The presence of a foreign body potentiates the infectivity of bacteria. In 1957, Elek and Conen³⁸ demonstrated that a single braided silk suture significantly reduces the inoculum of staphylococci required to produce a local infection. The risk of

BOX 49.1

Clinical Classifications of Prosthetic Graft Infections

Time of Appearance After Implantation

- Early: <4 months
- Late: >4 months

Relationship to Postoperative Wound Infection (Szilagyi's Classification)

- Grade I: cellulitis involving the wound
- Grade II: infection involving subcutaneous tissue
- Grade III: infection involving the vascular prosthesis

Extent of Graft Involvement (Bunt's Classification Modified)

- Arterial graft infection:
 - P0 graft infection: Infection of a cavitary graft (e.g., aortic arch; abdominal and thoracic aortic interposition; aortoiliac, aortofemoral, iliofemoral graft infections)
 - P1 graft infection: Infection of a graft whose entire anatomic course is noncavitory (e.g., carotid–subclavian, axillo–axillary, axillofemoral, femorofemoral, femoropopliteal/tibial)
 - P2 graft infection: Infection of the extracavitory portion of a graft whose origin is cavitary (e.g., infected groin segment of an aortofemoral or thoracofemoral graft, cervical infection of an aortocarotid graft)
 - P3 graft infection: Infection involving a prosthetic patch angioplasty (e.g., carotid and femoral endarterectomies with prosthetic patch closure)
- Graft-enteric erosion (GEE)
- Graft-enteric fistula (GEF)
- Aortic stump sepsis after excision of an infected aortic graft

foreign body infection is enhanced in the presence of a larger inoculum, more virulent bacterial strains, depressed host immune function, and invasion of sites more remote from host defenses.

Cellular and Biomolecular Events

The pathogenesis of biomaterial-associated infection involves the following fundamental steps: (1) adhesion of bacteria to graft or stent surfaces; (2) formation of microcolonies within a bacterial biofilm; (3) activation of host defenses (neutrophil chemotaxis, complement activation); and (4) an inflammatory response involving perigraft tissues and the graft-artery anastomoses.

After adherence of bacteria to the biomaterial surface, both graft and bacterial characteristics influence the likelihood of colonization. Bacterial adherence to polyester grafts is 10 to 100 times greater than adherence to polytetrafluoroethylene (PTFE) grafts. Gram-positive bacteria, such as staphylococci, produce an extracellular glycocalyx, or mucin, that promotes adherence to biomaterials in greater numbers than are seen with Gram-negative bacteria. The increased adhesion of staphylococci to biomaterials is due to specific capsular adhesions that mediate the attachment and colonization of microorganisms. The vascular prosthesis and adherent bacteria together stimulate the immune system through inflammatory

cytokines. The local inflammatory response after implantation serves to establish connective tissue ingrowth (“incorporation”) to the outer surface of the graft material. This healing process can be impaired by early perigraft seroma or hematoma formation, which increases the risk for bacterial adherence and colonization. The inflammatory response also creates an unfavorable healing environment characterized by local ischemia and an acidic pH that is potentially conducive to bacterial colonization. Local disruption of the fine balance between pro- and anti-inflammatory mediators may lead to excess production of matrix metalloproteinases (MMPs) by tumor necrosis factor-stimulated macrophages.³⁹ Excessive degradation of secreted extracellular matrix and angiogenic growth factors by MMPs may hinder optimal graft healing by restricting capillary ingrowth, tissue incorporation, and potential luminal endothelialization. Lack of perigraft ingrowth and vascularity also favors greater exposure of the implanted biomaterial to bacteria and sequestration within graft pores/interstices away from activated phagocytic cells. Neutrophil function can also be directly impaired in the presence of biomaterials. Decreased neutrophil opsonic, phagocytic, and bactericidal activity against *Staphylococcus aureus* has been observed in PTFE tissue cages implanted subcutaneously in guinea pigs.⁴⁰

Clinical Sources of Infection

Exposure of a vascular prosthesis to microorganisms (bacteria or fungi) can result in clinical infection by any of four mechanisms: perioperative contamination via the surgical wound; bacteremic seeding; mechanical erosion into the bowel, genitourinary tract, or through the skin; and involvement in a contiguous infectious process. Underlying impairment of host defenses can further increase the risk for infection.

Perioperative Contamination

Skin and lymph nodes are major reservoirs of bacteria. Biomaterial surfaces can contact microorganisms (1) by a direct route during implantation, (2) through the surgical wound, or (3) by hematogenous or lymphatic sources arising from remote sites of infection. Potential sources of direct graft contamination include breaks in aseptic operative technique and contact with a patient's endogenous flora harbored within sweat glands, lymph nodes, diseased arterial walls (atherosclerotic plaque or aneurysm thrombus), disrupted lymphatics, and intestinal bag effluents as well as injury to the gastrointestinal or genitourinary tract. Reoperative and urgent/emergent vascular procedures and prolonged operative time also increase the risk of vascular surgical site infections (VSSIs).⁴¹

If the surgical wound does not develop a fibrin seal or heal promptly after surgery, the underlying vascular prosthesis is susceptible to colonization from any superficial wound complication (cellulitis, dermal necrosis, lymphocele). Wounds with persistent drainage indicate the presence of ischemia or tissue injury that can extend to deeper tissue and involve the

prosthesis. Diseased arterial walls and reoperative wounds are an unappreciated source of bacteria, with microbiologic culture recovering pathogenic strains of staphylococci in 10% to 20% of cases.¹ Bacteria can be harbored in scar tissue or lymphoceles of healed wounds and can contact prosthetic grafts undergoing revision or arterial replacement. Culture of explanted graft material from such procedures has isolated microorganisms, typically *S. epidermidis*, from 50% to 70% of thrombosed grafts and from more than 80% of grafts associated with anastomotic aneurysms.⁴²

Bacteremia

Bacterial seeding of the prosthesis via a hematogenous route is an uncommon but important mechanism of graft and stent infection. Experimentally, intravenous infusion of 10^7 colony-forming units of *S. aureus* administered within days of implantation produces a clinical graft infection in nearly 100% of animals.⁴³ Thus bacteremia arising from infected intravascular catheters, urinary tract infection, pneumonia, or infected foot wounds increases the risk of graft infection.

Parenteral antibiotic therapy has been shown experimentally to significantly decrease the risk of graft colonization from bacteremia and this is the rationale for both antibiotic prophylaxis and culture-specific antibiotic therapy in patients with a known site of infection. As the prosthesis heals and becomes incorporated into surrounding tissue, susceptibility to bacteremic colonization decreases but vulnerability has been documented more than 1 year after implantation, with infection developing as a result of dental and gastrointestinal diagnostic procedures. Transient bacteremia, in conjunction with altered immune status, may account for some graft infections occurring years after the original operation.

Mechanical Erosion

Erosion of a prosthetic graft through the skin or into the gastrointestinal or genitourinary tract results in a perigraft infection that can spread along the length of the graft. Graft-enteric erosion/graft-enteric fistula (GEE/GEF) can develop as a result of pulsatile movement of an aortic graft against adjacent bowel, most commonly without adequate intervening retroperitoneal soft tissue. Enteric erosion may involve the graft body or anastomotic sites with intact suture lines or pseudoaneurysm formation. A low-grade underlying graft infection has been found in a fraction of cases (confirmed by operative findings and recovery of staphylococcal species) and may provide an additional inflammatory stimulus for bowel adhesion.⁴⁴ The reported incidence of GEE/GEF after prosthetic aortic grafting is 0.4% to 2%.

Involvement by a Contiguous Infectious Process

Prosthetic grafts can become colonized as a result of an adjacent infection. The most common clinical scenarios are an aortofemoral graft limb infection associated with diverticulitis and a peripheral graft infection secondary to an infected lymphocele. Frequently the graft segment adjacent to the contiguous bowel or soft tissue infection may be involved.

Impaired Host Defenses

Impaired host defenses from underlying systemic conditions can also predispose patients to prosthetic graft infection.⁴⁵ The altered immune function associated with malnutrition, malignancy, lymphoproliferative disorders, autoimmune diseases, chronic renal insufficiency/uremia, advanced liver disease, drug administration (corticosteroids, antineoplastic and immune-modulating agents), and potentially diabetes mellitus may potentiate graft infection with lower numbers of contaminating bacteria.

Bacteriology

Although any microorganism can infect a vascular prosthesis, *S. aureus* is the most prevalent pathogen and accounts for 25% to 50% of infections, depending on the implant site (Table 49.2). Graft infections with *S. epidermidis* or Gram-negative bacteria have increased in frequency. This change in the microbiology of graft infection is the result of reporting of both early- and late-appearing graft infections, including aortic graft infections associated with GEE/GEF. Coagulase-negative staphylococci are present in normal skin flora but have the ability to adhere to and colonize biomaterials, where growth occurs within a biofilm on the surface of prostheses. Surgeons have also become aware of microbiologic sampling errors in late infections because of low numbers of bacteria present within the graft surface biofilm and their slow growth.⁴⁶ Graft infections associated with negative culture results are caused by *S. epidermidis* or other coagulase-negative staphylococci and by *Candida* species. Infection with Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas*, *Klebsiella*, *Serratia*, and *Proteus* species can be particularly virulent. The incidence of anastomotic dehiscence and arterial rupture is high because of the ability of the organisms to produce destructive endotoxins (elastase and alkaline protease) that compromise the structural integrity of the vessel wall. Fungal (*Candida* and *Aspergillus* species) and mycobacterial (tuberculous) infections of grafts are rare, and most patients with such infections are either severely immunosuppressed or have an established fungal or opportunistic infection elsewhere.

Plasmid-mediated genetic mutations have afforded *S. aureus* resistance against penicillin, β-lactams, and other antibiotics (aminoglycosides, erythromycin, tetracycline). Nosocomial and community-acquired infections caused by methicillin-resistant *S. aureus* (MRSA) have rapidly increased in prevalence over the past 15 years. Although estimates in the general population have shown MRSA skin colonization (nares and wounds) in less than 2% of individuals, a much higher prevalence is found in residents of long-term care facilities (23%–49%).^{47–49} A study involving more than 13,000 surgical patients admitted to a tertiary hospital in Switzerland found that the overall incidence of MRSA carriers was 4%, but of those carriers, 64% were newly identified. Previous hospitalization, age greater than 75 years, and recent antibiotic treatment were each prognostic for unsuspected MRSA carriage.⁵⁰ The combination of increased prevalence, harboring in high-risk populations, multiple staphylococcal virulence factors, and rapidly evolving antibiotic resistance mechanisms makes emergence of MRSA a daunting medical challenge. British reports have documented MRSA as the most common pathogen involved in vascular wound and graft infections and concluded that it is associated with higher morbidity and mortality rates than infection with other microbes.^{51,52} At the University of South Florida (USF), the prevalence of MRSA arterial graft infections increased four-fold over a 25 year span (from 11% before 2000 to 49% after 2000), with more than half of early extracavitary graft infections being the result of MRSA. Early mortality, limb loss, and infection recurrence rates have not been appreciably higher for MRSA in the USF experience. However, the future possibility of a higher overall incidence of graft or vascular device infections caused by more prevalent MRSA colonization in the vascular population is concerning.

Prevention Principles

Surgical site infection (SSI) guidelines have recently been updated and a comprehensive review has been generated by the American College of Surgeons and the Surgical Infection Society.⁵³

TABLE 49.2 Bacteriology of Prosthetic Vascular Graft Infections from Collected Series

Microorganism	Thoracic Aorta	INCIDENCE (%)			
		Graft-Enteric Erosion/ Graft-Enteric Fistula	Aortofemoral	Femoral/Popliteal/ Tibial	Carotid
<i>Staphylococcus aureus</i>	32	4	27	28	50
<i>Staphylococcus epidermidis</i>	20	2	26	11	15
<i>Streptococcus</i> spp.	2	9	10	11	3
<i>Pseudomonas</i> spp.	10	3	6	16	6
Coliforms/Gram-negative organisms ^a	14	49	28	29	9
Other species/Candida	10	15	1	3	5
No growth/no culture	12	18	2	2	12

^a*Escherichia coli*; *Enterococcus*, *Bacteroides*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus* species.

VSSIs can be minimized if the following principles are applied:

1. Avoid a prolonged preoperative hospital stay to minimize the development of more resistant hospital-acquired bacterial strains.
2. Have patients shower, scrub, or wipe with an alcohol-based soap (e.g., chlorhexidine) for 1 to 3 days before the operation.
3. Control remote infections before an elective vascular operation.
4. Remove hair from the operative site immediately before the operation with care to avoid skin trauma.
5. Protect vascular grafts from contact with exposed skin in the operative field by using iodine-impregnated plastic drapes or antibiotic-soaked towels/sponges.
6. Avoid concomitant gastrointestinal procedures during cavitary grafting procedures.
7. Use prophylactic antibiotics (30–60 minutes before skin incision) prior to open surgical implantation of a prosthetic graft.
8. Longer (>24 hours) duration of periprocedural antibiotics may be considered when two or more patient-related high-risk factors for surgical wound infection are identified, including extremes of age, malnutrition, prolonged hospitalization, remote infections, immunosuppression, recent or “redo” operations, and previous irradiation of the surgical site.
9. Measures aimed at controlling MRSA include the use of disposable barriers (gowns, gloves, masks) by all individuals contacting MRSA carriers to reduce direct transmission within hospitals, routine MRSA screening (nares swab) of all admitted patients, and use of nasal mupirocin ointment and repeated chlorhexidine skin cleansing before operations.
10. Meticulous attention to sterile technique. Careful handling of tissues, prevention of hematoma formation, and closure of groin incisions in multiple layers to eliminate dead space with lymphatic resection/ligation are imperative to reduce wound complications. Skin reapproximation without tension minimizes the development of dermal ischemia and wound edge necrosis.

Topical Antibiotics

The addition of topical antibiotics (bacitracin or cefazolin) to irrigating solutions allows soaking of grafts before implantation and cleansing of wounds before closure and may contribute to decreased wound infection rates. Randomized clinical trials using rifampin-soaked (1 mg/mL) gelatin-impregnated polyester aortofemoral grafts have reported significantly reduced groin wound infection rates (4.4% without rifampin vs. 2.7% with rifampin), although the rates of subsequent graft infections were similar (0.6% vs. 0.3%).^{54,55} All graft infections were caused by *S. aureus* in this study. On the basis of the absence of a longer-term benefit, routine rifampin treatment of polyester grafts for primary aortic reconstruction cannot currently be recommended.

Prophylactic Antibiotics

Prophylactic antibiotics should be infused before skin incision and at regular intervals during long procedures (>3 to 4 hours) to maintain tissue drug levels above the minimal bactericidal concentration for expected pathogens (Box 49.2). Prophylaxis should also be instituted before percutaneous puncture of existing prosthetic grafts (peripheral or coronary arteriography accessed through existing femoral grafts) or before selected endovascular interventions involving stent/stent-graft implantation. Culture-specific antibiotics should be prescribed for patients undergoing vascular graft implantation who have co-existing infections of the leg or another remote site.

After implantation of a prosthetic graft, patients should be informed of the potential risk for graft colonization and infection from transient bacteraemia, especially after dental work, colonoscopy, or cystoscopy. Antibiotic prophylaxis is recommended if these procedures are performed within 3 months of the vascular operation. Amoxicillin 2 g orally 1 hour before the procedure can be used. For patients with penicillin allergy, clindamycin 600 mg orally 1 hour before the procedure is an alternative.

DIAGNOSIS

The prompt diagnosis and treatment of prosthetic graft infections is essential to avoid major complications (advanced sepsis and hemorrhage) and death. Clinical manifestations are varied and may be subtle, particularly when associated with

BOX 49.2

Antibiotic Prophylaxis in Adults Undergoing “Clean” Prosthetic Graft or Patch Implantation and Selected Endovascular Procedures

- Pre-carotid endarterectomy, femoral reconstruction, AAA open repair, or EVAR:
Cefazolin 1–2 g IV 30 min before the procedure and repeated (1–2 g) q8h for 24 h or
Cefuroxime 1.5 g IV and q12h for 24 h
- Single prophylactic dose before any endovascular procedure involving a prior access-site prosthesis, repuncture of a recent access site, prosthetic/device reintervention (secondary intervention), or an existing remote peripheral arterial device (e.g., prior stents, grafts):
Cefazolin 1–2 g IV or cefuroxime, 1.5 g IV
- Before reoperation involving an existing prosthetic graft/patch:
Vancomycin 1 g IV given 30–60 min before incision and continued q12h for 24–48 h
- Known patient MRSA colonization or prolonged or recurrent stay in hospital or chronic care facility (high MRSA risk):
Vancomycin 1 g IV before the incision/procedure
- Alternatives for penicillin, cephalosporin, or vancomycin allergies:
Daptomycin 4 mg/kg IV before procedure and daily for 24–48 h
Levofloxacin 500 mg IV before the procedure and then daily for 24–48 h
Clindamycin 900 mg IV before the procedure and then 450–900 mg q8h for 24–48 h

AAA, abdominal aortic aneurysm; EVAR, endovascular stent-graft AAA repair; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

late-appearing cavitary graft infections. The urgency of diagnostic evaluation depends on the clinical findings and the status of the patient.

Clinical Manifestations

Vascular surgeons should maintain a low threshold for proceeding with additional diagnostic testing when any symptom or sign suggests graft infection. In aortic grafts confined to the abdomen, unexplained sepsis, ileus, or abdominal distention might be the only clinical sign. If infection involves an extra-cavitory graft, the initial sign of infection is usually overlying inflammation/cellulitis, a cutaneous draining sinus tract, or an anastomotic pseudoaneurysm. Any patient with gastrointestinal bleeding and an aortic graft should be presumed to have graft infection and GEE/GEF until either another source of bleeding is conclusively identified on endoscopy or no graft–bowel communication is verified at surgery.

In patients with vague suggestive symptoms and ultrasound or computed tomography (CT) evidence of perigraft fluid, a thorough clinical history may furnish clues that further support the diagnosis of graft infection and provide the rationale for invasive diagnostic testing. The patient should also be queried about recent medical illnesses that may have resulted in hematogenous or lymphatic seeding of the graft with bacteria. Early graft infections with *S. aureus* or other Gram-negative bacteria typically manifest within weeks of the procedure as fever, leukocytosis, wound complications, and perigraft purulent drainage. Bacteremia is a sign of an advanced graft infection associated with arterial wall or mural thrombus infection or the secondary development of endocarditis. Patients with grafts infected by *S. epidermidis* are typically seen years after graft implantation with graft-healing complications (anastomotic aneurysm, perigraft fluid cavity, or graft–cutaneous sinus tract). Signs of systemic sepsis are frequently absent.

An elevated white blood cell (WBC) count with a left-shifted differential count and an increased erythrocyte sedimentation rate are common but nonspecific findings in patients with graft infection and fever. Routine laboratory testing should also include urinalysis, blood culture, and cultures of other clinical sites of infection such as foot ulcers and surgical wound drainage. Positive blood culture results are uncommon (<5%), but when present they indicate an advanced graft infection, virulent organisms, or both. All laboratory test results may be normal in patients with late-appearing perigraft infections with *S. epidermidis*.

Imaging Studies

Vascular imaging is essential for the diagnosis and treatment of graft infection and its sequelae. Anatomic signs of graft infection – such as perigraft abscess, anastomotic aneurysm, and GEE/GEF – can be accurately identified (with >90% sensitivity) through a combination of CT and endoscopy. Vascular imaging studies permit localization of involved prosthetic infection, related operative sites/tissues for abnormal healing and facilitate planning of surgical treatment options.

Contrast-Enhanced Computed Tomography and Computed Tomographic Angiography

CT is the preferred initial imaging technique for suspected graft infections in aortofemoral and abdominal vessels as well as the thoracic aorta and major cavitary branch vessels (P0, P2) (see Ch. 29, Computed Tomography). CT is also preferred for cavitary graft infections involving the neck, torso, and proximal parts of the limbs (P1, P3). It should be performed with and without intravenous contrast with oral contrast agents (to detail the relationship of adjacent enteric structures) used only in patients in whom GEE/GEF is suspected. The exact location and extent of polyester and PTFE grafts can best be seen on initial non-contrast-enhanced imaging. Review of delayed arterial-phase images or the “bone” preset window for early arterial-phase imaging best separates the detail of prosthetic graft, arterial, and venous structures from perigraft tissues and aids in image interpretation.

Diagnostic criteria consistent with infection include the loss of normal tissue planes (fat density) of the retroperitoneal or subcutaneous perigraft structures (indicative of inflammation), collections of fluid or gas around the graft (Fig. 49.1), the formation of false aneurysms, hydronephrosis, and adjacent vertebral or bony osteomyelitis. Any gas in periprosthetic tissues beyond 2 or 3 months after implantation is an abnormal CT finding suggestive of graft infection. CT angiography provides an assessment of continuity of the arterial lumen, associated



Figure 49.1 Non-contrast-enhanced CT scan showing an infected aortofemoral graft limb (arrow). (A) Perigraft fluid and inflammation in the groin. (B) Infection-associated ipsilateral hydronephrosis, indwelling ureteral stent, and atrophic kidney.

distribution of occlusive disease, the presence of thrombus at planned clamp sites and permits operative planning for arterial reconstruction without invasive arteriography.

Ultrasonography

Ultrasonography can be performed urgently as a portable bedside examination in severely ill patients. It should be the initial imaging study for extracavitory (P1, P2, P3) graft infections. Color duplex scanning can reliably differentiate a perigraft fluid collection from an anastomotic pseudoaneurysm, hematoma, and soft tissue masses (enlarged lymph nodes). Ultrasonography has the advantage of being the most accurate vascular imaging technique for verifying vessel or graft patency and assessing pulsatile masses adjacent to grafts in the groin and limbs (see Ch. 22, Vascular Laboratory: Arterial Duplex Scanning).

Magnetic Resonance Imaging

MRI provides anatomic imaging equivalent to that of CT but is better able to distinguish between perigraft fluid and fibrosis on the basis of differences in signal intensity between T1- and T2-weighted images (see Ch. 30, Magnetic Resonance Imaging and Arteriography). A gadolinium contrast agent enhances vascular luminal resolution (magnetic resonance angiography, or MRA) to allow planning of arterial reconstruction. Although less nephrotoxic than iodinated contrast agents, gadolinium has unfortunately been linked to a systemic fibrotic process in patients with renal insufficiency.

Functional White Blood Cell Scanning

All radionuclide imaging techniques aim to demonstrate abnormal accumulations of leukocytes in perigraft tissue for the diagnosis of graft infection, but they do not provide anatomic detail. However, they can be correlated with MRI and CT to delineate the anatomic extent of infection. The type of radionuclide used (gallium 67 citrate, indium-111-labeled leukocytes, technetium Tc-99m hexametazime-labeled leukocytes) can vary and will affect diagnostic accuracy. The accuracy (positive predictive value) of indium-111-labeled WBC scans approaches 80% to 90% in detecting graft infection. Functional WBC scans are not useful, however, during the early postoperative course (3–6 months) because of nonspecific radionuclide uptake in the healing and inflamed perigraft tissue, resulting in a potential false-positive result. Normal scans (those showing no labeled WBC accumulation) have been reported in late-appearing aortic graft infection and documented cases of GEE/GEF (both false-negative results).

Endoscopy

With use of upper endoscopy, an important diagnostic modality for suspected GEE/GEF, the lumen of the esophagus, stomach, entire duodenum, and ideally the proximal jejunum can be inspected for sources of bleeding (a pediatric colonoscope should be used).

Computed Tomography – Guided Aspiration Versus Operative Findings

CT-guided aspiration of cavitary perigraft fluid collections is increasingly being used to differentiate uninfected seroma

from abscess formation. Sampling error (limited sampling in septated perigraft fluid collections) is possible with percutaneous aspiration techniques, as is misinterpretation of negative culture results as indicating no graft infection in some cases of *S. epidermidis* biofilm infection. The definitive diagnostic test for suspected graft infection is operative exploration, especially with equivocal anatomic imaging results and suspected GEE/GEF. Direct exposure of the outer surface of the biomaterial through the typically thick fibrous capsule encompassing a polyester graft allows the detection of late indolent biofilm infections.

Culture Techniques

Standard swab cultures of material taken directly from the graft surfaces and perigraft fluid are usually sufficient in patients with obvious local or systemic sepsis caused by more virulent organisms, which are usually present in high numbers. However, surface swabs may not recover less virulent pathogens that do not invade perigraft tissues. An apparent negative result of Gram staining of tissue or fluid from around an unincorporated prosthetic graft showing no organisms (but typically the presence of WBCs) is not sufficient to exclude a low-grade graft infection because low numbers of slow-growing bacteria can reside within a surface biofilm.

For reliable recovery of microorganisms from within a biofilm infection, mechanical (tissue grinding) or ultrasound disruption of the biofilm of an explanted graft segment must be performed before incubation in a broth culture medium. Placement of a small graft segment in a trypticase soy broth medium is believed to maximize bacterial growth and recovery because the liquid medium allows submersion of the graft and optimal exposure of any adherent bacteria to the nutrient medium. The use of mechanical disruption and broth cultures is particularly helpful in confirming graft infection with *S. epidermidis*. Culture tubes should be maintained for 5 to 7 days to exclude growth.

SURGICAL TREATMENT AND OUTCOMES

Treatment Considerations

The goals of managing vascular graft infections include initial and long-term eradication of the local and systemic septic process and maintenance of normal arterial perfusion to involved end-organ and limb tissues. Our USF group advocates a patient-specific treatment algorithm involving the use of conventional (total graft excision and extra-anatomic/remote bypass) or *in situ* replacement modalities and, occasionally, graft preservation techniques.⁵⁶

Selection criteria for specific treatment modalities are based primarily on the clinical findings, extent of graft involvement, and microbiology (Table 49.3). Important adjuncts to attain wound sterilization for a VSSI, especially when *in situ* reconstruction or graft preservation is under consideration, include the use of multiple staged debridement and/or “washout” operative procedures

TABLE 49.3 Selection Criteria for Appropriate Operative Management of Prosthetic Vascular Graft Infection

Treatment Option	Manifestations	Extent of Infection	Microbiology
Graft preservation/local therapy	Early infection, no sepsis	Not Dacron, graft body only, no anastomosis, segmental	Gram-positive organism, <i>Staphylococcus</i> spp.
Graft excision only	Graft thrombosis, viable limb, adequate collaterals	Any	Any organism
Excision and Ex Situ Bypass			
Simultaneous	Unstable patient, GEE/GEF, hemorrhage, severe sepsis	Invasive infection	Any organism
Staged	Stable patient, mild sepsis, GEE/GEF, no active bleeding	Invasive infection	Any organism
In Situ Replacement			
Prosthetic	No sepsis, no GEE/GEF	Biofilm infection, segmental	<i>Staphylococcus epidermidis</i> , not Gram-negative organism or MRSA
Autologous vein	No sepsis, no GEE/GEF, severe occlusive disease	Invasive or biofilm, diffuse or segmental	Not <i>Pseudomonas</i> , <i>Serratia</i> , <i>Proteus</i> , <i>E. coli</i> , <i>Klebsiella</i>

GEE, graft-enteric erosion; GEF, graft-enteric fistula.

(every 3–4 days) to minimize residual bacterial counts with more virulent infections; aggressive excision of involved arterial wall and perigraft tissues to healthy tissue planes; intraoperative mechanical and passive wound irrigation with cytotoxic agents (pulsed Clorpactin, passive dilute Betadine plus peroxide); temporary placement of antibiotic-loaded beads; soft tissue coverage of arterial repairs with uninfected, well-vascularized rotational muscle or fasciocutaneous flaps or omental pedicles; negative-pressure wound “sponge” (VAC) therapy; closed suction drains and continuous dilute Betadine irrigation in grossly infected tissue beds; and culture-specific parenteral antibiotics.

Several general treatment tenets are imperative. Infection involving prosthetic biomaterials frequently requires partial or complete graft removal to eradicate the local septic process. Attempts to preserve prosthetic grafts are appropriate only in limited circumstances. Graft preservation is possible for most arterial infections involving autologous tissue reconstruction (vein bypass or patch). As noted by Calligaro and colleagues⁵⁷ at USF, we have experienced successful graft preservation attempts with early-appearing extracavitory prosthetic infections and overall equivalent outcomes (operative mortality or limb loss) in early and late graft infections with use of a selected treatment regimen. The exception for preservation efforts is invasive infections (those producing local and systemic sepsis) caused by virulent *Pseudomonas*, *Klebsiella*, *Serratia*, *Proteus* species, and *E. coli*. Autologous or prosthetic graft excision with *ex situ*/extra-anatomic revascularization is indicated in these scenarios.

Cavitory graft infections are less amenable than extracavitory infections to wound sterilization techniques involving multiple debridement procedures. Instead, a definitive procedure (simultaneous debridements) or two (staged) procedures that include total graft excision and *in situ* or *ex situ* reconstruction are required for cavitory infections. Because of the added invasiveness and physiologic stress of repeated cavitory exposure for the treatment of abdominal or thoracic graft infection, potential catastrophic cavitory

graft disruption, and risk of development of enteric erosion or fistulization in the infected graft, preservation techniques should be attempted only rarely for cavitory graft infections.⁵⁸ A recommended treatment algorithm for cavitory graft infections is provided and described at the end of this chapter.

Graft Preservation

Attempts at graft preservation with just local measures are possible in limited circumstances. Patent grafts with infection involving a shorter length (segmental) and sparing anastomoses (graft body only) can be considered for preservation. Results have been better with PTFE than with polyester conduits, with early (<4 months after implantation) rather than late (>4 months) infectious manifestations, with single Gram-positive organisms than with polymicrobial or Gram-negative infections, and with extracavitory rather than cavitory locations. Graft preservation should be attempted only for infections that are limited to the immediate perigraft region, caused by bacteria with low virulence and not associated with systemic sepsis.

Serial wound debridement in the operating room, use of cytotoxic irrigating solutions, and placement of antibiotic-loaded polymethyl methacrylate (PMMA) beads are necessary steps to minimize residual bacterial counts. Residual negative wound culture results are necessary for eventual rotational muscle flap coverage of the exposed graft segment, definitive skin closure, or both. More aggressive attempts at graft salvage by others, not necessarily adhering to the aforementioned criteria, have achieved complete graft preservation and wound healing in roughly 70% of patients with early aortofemoral graft limb⁵⁹ or infrainguinal prosthetic bypass infections.²¹ However, initial treatment failures as a result of fatal graft disruption, persistent graft infection, and nonhealing wounds in 30% of cases limit broader application of this approach and emphasize the need to perform graft excision if local sepsis persists during serial treatments.¹¹ Mayer et al.,⁶⁰ advocating the

use of debridement and negative-pressure wound therapy applied directly to exposed reconstructions for Szilagi grade III (deep) infections, achieved 91% wound healing and 84% freedom from reinfection. However, in that cohort only 54% involved prosthetic graft infection. By comparison, with use of our stricter selection criteria, only 15% to 20% of our USF patients with early extracavitary prosthetic graft infections were deemed candidates, and they were successfully treated by preservation techniques.

Graft Excision And Extra-Anatomic Bypass

Need for Revascularization

Graft excision without revascularization may be possible in some cases, including those in which claudication was the initial indication for intervention and when thrombosis of an infected graft does not result in critical limb ischemia. Arterial collaterals around a thrombosed or ligated bypass may take several weeks to develop, and inflow may be optimized by endovascular intervention if occlusive lesions are present in the native proximal vessels. Such an approach may be possible for a localized/segmental groin infection and aortofemoral graft via ligation of the affected limb through a clean retroperitoneal incision, segmental graft excision through the groin wound, endovascular recanalization of residual aortoiliac stenoses/occlusions, and femoral artery vein patch (**Fig. 49.2**).

Intraoperative decisions regarding the need for immediate revascularization in patients with patent, infected grafts can be made with the use of temporary bypass occlusion, a sterile blood pressure cuff, and continuous-wave Doppler assessment of pedal outflow. Persistence of a pulsatile pedal arterial signal and ankle pressure greater than 40 mm Hg with bypass occlusion may allow initial graft excision and consideration of delayed revascularization after eradication of local infection. Absence of pulsatile pedal flow during temporary bypass occlusion would probably result in critical ischemic symptoms and risk of limb loss, thus mandating concomitant limb revascularization.

Graft Excision

Conventional management of an infected prosthetic arterial bypass involves total graft excision and revascularization via extra-anatomic/remote routes (*ex situ*) through uninfected tissue planes. This approach is generally required in patients with GEE/GEF and for more invasive infections associated with systemic sepsis or extensive perigraft infection (retroperitoneal/psoas abscess). Complete removal of diffusely infected aortoiliofemoral grafts (including anastomotic suture lines) is accomplished by repeat celiotomy or a left retroperitoneal exposure. The explanted graft material should always be cultured.

Proximal control/clamping of the supraceliac aorta may be necessary during exposure of an infrarenal anastomosis with significant retroperitoneal inflammation. Occluding Fogarty balloons may be used into patent iliac systems for hemostatic control. Ureters should be identified and protected during pelvic dissection, and preoperative placement of ureteral stents may be helpful to avoid injury when hydronephrosis and extensive retroperitoneal inflammation are present. The infrarenal aorta should be debrided back to normal-appearing wall. Pledgets of prosthetic material should be avoided, and a double layer of interrupted monofilament suture should be used for aortic ligation. Occasional sacrifice of a renal artery origin (with or without revascularization from a supraceliac aortic prosthetic bypass) may be needed when pararenal aortic infection/inflammation is present and clean stump closure proves difficult. A similar closure technique for the distal aortic or iliac arteries should be performed to maintain retrograde flow from extra-anatomic bypasses at the femoral level into at least one pelvic artery system (external iliac and hypogastric) to avoid pelvic ischemia.

Aggressive excisional debridement of infected perigraft tissue along with irrigation with cytotoxic agents and tunneling and placement of an omental pedicle to cover the aortic stump and retroperitoneal wound may reduce the risk of residual infection and later catastrophic “stump blowout.” Temporary closed-suction drains and continuous dilute Betadine irrigation

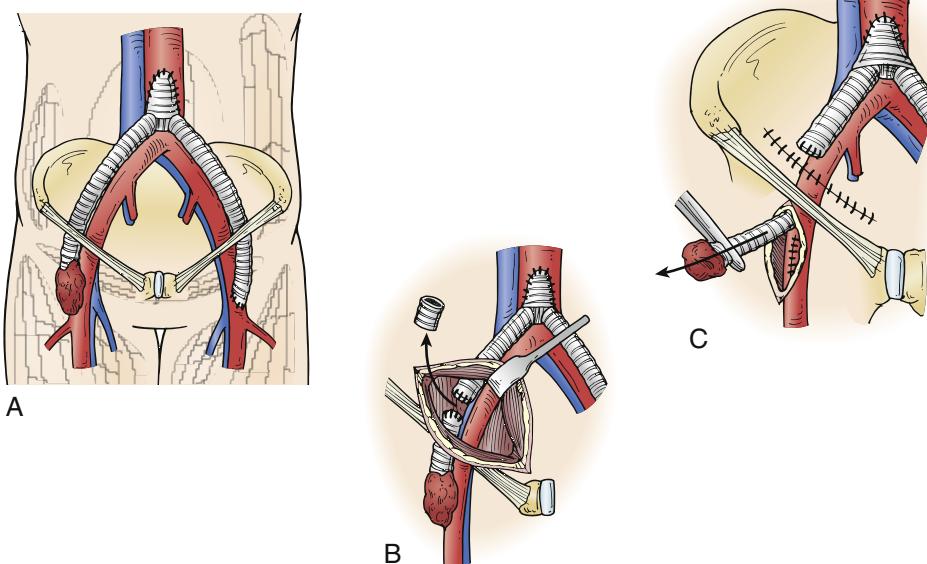


Figure 49.2 Excision of an infected distal aortofemoral graft segment. (A) Localized/segmental distal graft groin infection. (B) Retrorperitoneal exposure of an uninfected graft limb through clean tissue planes. (C) Excision of an infected graft segment. *In situ* prosthetic or autologous vein replacement is performed if needed.

in the retroperitoneal wound bed can be considered in patients with abscess and extensive local infection. Repeat CT imaging within 7 to 10 days can confirm abscess cavity regression to allow removal of drains.

Timing of Limb Revascularization

In patients with aortic graft infection, the timing of limb revascularization depends on the clinical findings. Simultaneous *ex situ* bypass with graft excision is necessary in hemodynamically unstable patients with systemic sepsis, hemorrhage from dehiscence of the anastomosis, or GEE/GEF. However, staged management with initial axillofemoral PTFE bypass followed in 1 to 2 days by excision of the aortic graft has been associated with lower perioperative mortality than a simultaneous approach in stable patients.¹⁵

Several decades of experience with the conventional management of aortic graft infection has led to minimal changes in operative mortality but significant reductions in early limb loss, residual aortic stump infection and blowout, and recurrent infections involving *ex situ* prosthetic bypasses as well as improved midterm patient survival (Table 49.4).^{61,62} The highest mortality rates continue to occur in patients with GEE/GEF or systemic sepsis; conventional management is preferred over *in situ* replacement techniques for such patients.

Diffuse aortobifemoral graft infections involving the groin region and with significant associated femoropopliteal

occlusive disease can make *ex situ* approaches to revascularization challenging (Fig. 49.3). Limb loss is more frequent after aortofemoral graft infection than after aortoiliac reconstructions because of the higher risk for *ex situ* bypass thrombosis or recurrent infection. Unilateral axillofemoral bypasses to the profunda femoris or superficial femoral artery through an uninfected tissue plane have acceptable patency rates (94% at 6 months), but distal anastomoses to the popliteal artery are prone to early failure (42% at 6 months).⁶³ Preservation of retrograde flow into the common femoral artery by vein patching (and endarterectomy for occlusive disease) after excision of the infected aortofemoral graft is also important for maintaining pelvic flow. A further option for managing aortofemoral graft infection is a unilateral axillofemoral PTFE bypass through uninvolved/less involved tissue, autogenous deep vein cross-femoral bypass in infected fields, and total aortic graft excision.

In Situ Graft Replacement

Autologous Graft Replacement

The great saphenous vein (GSV) or a superficial upper extremity vein can be used for the reconstruction of infrainguinal, visceral, cervical, and upper extremity arteries after excision of an infected graft. However, use of GSV grafts for cross-femoral, iliofemoral, or common carotid/innominate replacement has resulted in limited patency because of size mismatch and occlusion from intimal

TABLE 49.4 Results of Treatment of Prosthetic Graft Infections Involving the Infrarenal Aorta or Aortoiliofemoral Bypass^a

GRAFT EXCISION AND EX SITU BYPASS							
Series	Year	Number of Patients	Operative Mortality (%)	Early Limb Loss (%)	Stump Blowout (%)	Survival >1 Year (%)	Extra-Anatomic Bypass ^b Infection (%)
O'Hara et al. ⁶	1986	84	18	27	22	58	25
Reilly et al. ¹⁵	1987	92	14	25	13	73	20
Yeager et al. ¹⁷	1999	60	13	7	4	74	10
Seeger et al. ⁶¹	2000	36	11	11	3	86	6
Bandyk et al. ¹⁰	2001	31	22	10	0	81	3
IN SITU REPLACEMENT							
Neo-aortoiliac System/Superficial Femoropopliteal Vein				Operative Mortality (%)	Early Limb Loss (%)	1-Year Graft Patency (%)	Survival >1 Year (%)
Nevelsteen et al. ²⁵	1995	29	9	6	90	83	1
Clagett et al. ¹²	1997						
Ali et al. ⁶⁸	2009	187	10	7	92	77	5
Prosthetic							
Bandyk et al. ¹⁹	2001	25	0	0	100	100	12
Allograft							
Kieffer et al. ⁶²	2004	179	20	0.5	80	74	3

^aSome series include cases involving graft-enteric erosion/graft-enteric fistula, which may influence the reported operative mortality.

^bCross-femoral, axillofemoral.

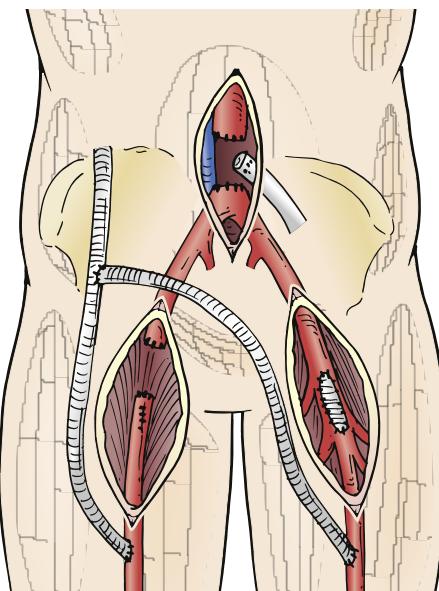


Figure 49.3 Excision of an infected aortobifemoral graft with extra-anatomic bypass.

proliferation.⁶⁴ Use of appropriate lengths of a femoropopliteal vein segment has allowed larger-diameter, autologous arterial reconstruction without causing significant morbidity in the donor limb (extensive deep venous thrombosis, limb edema, compartment syndrome) (Fig. 49.4). Preoperative ultrasonographic mapping of the GSV, arm vein, and the superficial femoropopliteal vein (SFPV) can be done in nonurgent scenarios to best match available autologous conduit and repair-site diameters. Adequacy of the femoral vein (absence of acute/chronic thrombus, diameter >5 to 6 mm) can be confirmed by ultrasound when a small-diameter GSV or arm vein (<4 mm) is seen.

Neo-Aortoiliac System Reconstruction

Construction of an *in situ* neo-aortoiliac system (NAIS) from SFPV after removal of an infected aortoiliofemoral graft was first described by Clagett et al.⁶⁵ and Nevelsteen et al.²⁵ Preoperative ultrasound mapping of the deep leg veins is recommended because long replacement lengths necessitate bilateral harvest. Longitudinal thigh incisions lateral to the sartorius muscle proximally and division of the adductor hiatus are needed, with double-ligation techniques to secure side branch origins. The vein is harvested distal to the profunda femoris origin of the common femoral vein, preserving collateral venous outflow. Prophylactic lower-dose anticoagulants (e.g., heparin) are recommended, as are sequential compression devices applied to the calf regions to augment venous outflow and limit propagation of thrombus in the ligated segments. Patients with prior GSV harvest undergoing SFPV harvest are at higher risk for the development of calf compartment syndrome (up to 12% incidence), so a low threshold for calf fasciotomy should be maintained. Late venous insufficiency and chronic limb edema affects 15% of patients.

SFPV segments are used in a nonreversed configuration after vessel eversion and direct excision of valve cusps. *In situ* replacement after graft excision and perigraft debridement can be tailored depending on the length of reconstruction needed and available SFPV (Fig. 49.5). If a wide infrarenal aorta is

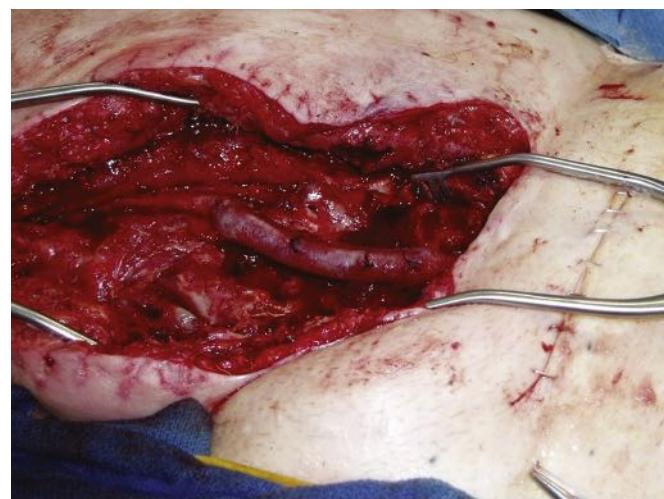


Figure 49.4 Interposition (*in situ*) replacement with a femoral vein segment after excision of an infected femoral prosthetic graft.

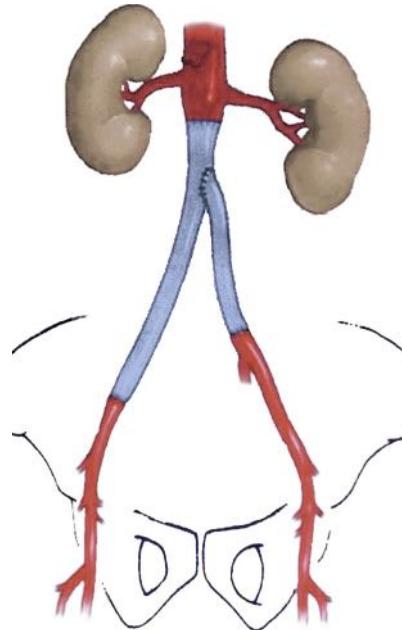


Figure 49.5 Schematic of deep venous replacement (neo-aortoiliac system) after excision of an infected aortobi-ilial prosthetic graft. Shortening of the total bypass length (and necessary bilateral femoral vein harvest) is possible because the contralateral femoral vein segment (to the left leg) originates off the mid or distal region of the ipsilateral aortoiliofemoral graft (to the right leg). (From Jackson MR, et al. Excision and autogenous revascularization of an infected aortic stent graft resulting from a urinary tract infection. *J Vasc Surg*. 2002;36:622.)

present (18–26 mm), a “pantaloons” technique can be used, in which two SFPV segments are sutured together over half of their circumferences proximally to widen the conduit for end-to-end aortic anastomosis. Excessively large aortic necks (>28 mm) may require ligation and *ex situ* bypass. If bilateral aortofemoral reconstruction is needed in patients in whom limited lengths of SFPV are available, a unilateral aortofemoral SFPV segment can be used with a shorter cross-femoral SFPV segment between the longer limb and the contralateral groin.

When compared with excision/*ex situ* bypass, *in situ* SFPV replacement for diffuse aortoiliofemoral graft infection has

been associated with lower mortality and amputation rates, improved graft patency rates, and a lower incidence of recurrent infection (see Table 49.4).¹² Longer-term audits of SFPV replacement by Clagett et al.^{65–68} show a primary graft patency rate of 81%, a secondary/assisted patency rate of 91%, and a freedom from amputation rate of 89% at 6 years. This treatment approach has an operative mortality rate of 10% and a 5-year survival of 52%. Early deaths and/or recurrent/residual vein conduit infection and disruption occurred after treatment of GEE/GEF or identification of virulent Gram-negative organisms. *In situ* SFPV replacement is therefore contraindicated under these circumstances. Vein conduit restenosis has been more common with a smaller-diameter femoral vein (<7 mm) and in patients with coronary disease or a history of smoking.⁶⁶

Antibiotic-Treated Prosthetic Grafts

Use of a prosthetic conduit for *in situ* replacement of infected grafts is a treatment option in selected circumstances. *In situ* prosthetic replacement with PTFE or polyester conduit has been associated with recurrent infection in 10% to 20% of cases, primarily with Gram-negative bacteria and MRSA involvement. These results have increased interest in antibiotic-bonded prosthetic grafts to potentially improve results.^{18,69,70}

We have advocated graft excision and *in situ* prosthetic replacement for localized/segmental, low-grade biofilm infections caused primarily by coagulase-negative staphylococci (*S. epidermidis*) (see Table 49.3). More than 50% of late extracavitory graft infections met these criteria and were treated with *in situ* PTFE graft replacement, with a recurrent infection rate of less than 5%.

Limited morbidity has also been shown with *in situ* replacement using PTFE and rifampin-soaked (60 mg/mL) gelatin-sealed Dacron for low-grade aortoiliofemoral graft infections (see Table 49.4).⁵⁶ Recurrent infections were due to rifampin-resistant *S. epidermidis*, MRSA, or more extensive graft involvement (bilateral graft limbs or aortic graft body), thus emphasizing that optimal results appear to be confined to limited biofilm infections (distal aortofemoral graft). Despite the risk of recurrent/residual infection, *in situ* prosthetic replacement of a distal aortofemoral graft limb through a groin incision may be preferred over cavitary graft excision and aortic reconstruction in debilitated elderly patients presenting with low-grade biofilm infection and local groin sepsis. Our selection criteria and treatment specifics for *in situ* prosthetic graft replacement are detailed in Box 49.3. Alternatively, Oderich et al.⁷¹ used *in situ* rifampin-soaked grafts with omental pedicle coverage to treat limited-involvement GEE/GEF (segmental enteric erosion onto aortic graft body or limb, no anastomosis/aneurysm, no retroperitoneal sepsis), reporting 9% early mortality and 4% reinfection rates. Partial excision of the existing aortic graft was possible in 43% of these selected cases.

Cryopreserved Arterial Allografts

A third option for *in situ* replacement is the use of aortic and iliofemoral arterial segments harvested from transplant donors and rendered nonantigenic by cryopreservation. Cryopreserved arterial allografts/homografts (CAHs) are now widely commercially available. Specific operative details for allograft implantation are provided in Box 49.4. Allograft replacement may have a primary role in mycotic or prosthetic graft infections of the thoracic or

BOX 49.3

Selection Criteria for and Treatment Components of *In Situ* Prosthetic Graft Replacement for Biofilm Graft Infection

Selection Criteria

- Clinical:
 - Late presentation (>4 months) after original graft implantation
 - No systemic signs of infection – afebrile, normal WBC count, sterile blood cultures
- Anatomic:
 - Limited local inflammation of tissue adjacent to the prosthetic graft
 - Perigraft cavity with absence of graft incorporation
 - Presence of graft–artery anastomotic pseudoaneurysm
- Microbiologic:
 - Perigraft fluid Gram stain with WBCs, no bacteria
 - Perigraft fluid culture with no growth
 - Graft biofilm culture – coagulase-negative staphylococci (*Staphylococcus epidermidis*)

Treatment Components

- Preoperative administration of vancomycin beginning 2–3 days before replacement
- Wide debridement/excision of inflamed perigraft tissue and the sinus tract if present
- Excision of anastomotic sites
- Cleansing/debridement of tissues and the retained graft segment with cytotoxic wound irrigation
- Use of rifampin-soaked (60 mg/mL) polyester gelatin or collagen-impregnated polyester grafts
- Muscle flap coverage of the replaced graft segment in the groin, omental pedicle coverage of intra-abdominal aortoiliac graft
- Parenteral administration of culture-specific antibiotics for 6 weeks

WBC, white blood cell.

BOX 49.4

Operative Details of the Use of Cryopreserved Arterial Allografts for Aortic Infection

1. Excise the infected vascular segments and perform perivascular debridement.
2. Thaw and rinse allografts immediately before implantation.
3. Use an appropriate length of allograft to perform a tension-free anastomosis.
4. Perform through-and-through ligature of allograft side branches – avoid the use of metal clips.
5. Use end-to-end anastomosis to native arteries or the retained prosthetic graft – avoid allograft-to-allograft anastomoses and use a single aortoiliofemoral allograft segment to fit the needed anatomic replacement.
6. Provide anastomotic reinforcement with allograft strips.
7. Use gentamicin-impregnated fibrin glue at the suture lines.
8. Use aggressive wound irrigation; consider drainage catheters, muscle flap coverage of the groin allograft, omental pedicle coverage of aortic allograft.
9. Prescribe 6 weeks of parenteral culture-specific antibiotics.

visceral aorta when *in situ* reconstruction is mandatory. Kieffer and colleagues reported an initial series in 1993 (36 patients)²⁴ and a more comprehensive experience in 2004 (179 patients)⁶² with allograft replacement for infrarenal aortic graft infection. The higher operative mortality was influenced by adverse outcomes in the 30% of patients with GEE/GEF (see Table 49.4).

The incidence of limb loss, recurrent infection, and midterm patient survival compares favorably with that for other methods of *in situ* replacement. However, allograft dilation/aneurysm formation (17%) or stenosis/occlusion (20%) occurred during late (>3 years) follow-up with earlier-generation CAH and fresh homografts. Three more recent studies document *in situ* CAHs used in 151 total patients for arterial infectious pathologies (96 with infected prosthetic aortic grafts) with an overall operative mortality of 10% and a 5% conduit-related complication rate (graft occlusion/stenosis, reinfection, degeneration) during 1 to 3 years of follow-up.^{72–74} However, using CAH as *in situ* replacement for peripheral arterial infections, Furlough et al.⁷⁵ reported a 30 day mortality rate of 9% and conduit-related complications within 2 years (anastomotic rupture, recurrent infection, occlusion, limb loss) in 30% of patients. These relatively poor results question any wider application of *in situ* CAH for treating extracavitary graft infections.

Treatment Adjuncts

Antimicrobial Agents

Parenteral antibiotics should be selected according to specific perigraft/graft culture results and adjustments should be made during serial/staged operations with repeated cultures obtained. Upon presentation with suspected graft infection, empiric broad-spectrum parenteral therapy is indicated with vancomycin (dosing adjusted to renal function and serum levels) and piperacillin/tazobactam 3.375 g every 6 hours, cefepime 2 g every 8 to 12 hours, or levofloxacin 500 mg daily (for penicillin/cephalosporin allergy). On the basis of culture and Gram stain results, biofilm (*S. epidermidis* or *S. aureus*) infections are treated with parenteral vancomycin, and we have abandoned adjunctive oral or intravenous rifampicin (potential emergence of resistant *S. epidermidis* with continued use). Invasive and persistent MRSA soft tissue infection should be treated with higher-dose daptomycin, 6 mg/kg daily. Pseudomonal infections should be “double-covered” with combinations of third- or fourth-generation cephalosporins, piperacillin/tazobactam, aminoglycosides, fluoroquinolones, or carbapenem/monobactams. Parenteral antibiotics should be continued for a minimum of 2 weeks. More invasive infections require 6 weeks of parenteral antibiotics. Oral amoxicillin/clavulanate or a fluoroquinolone can be used for 1–2 weeks for less invasive, non-MRSA infections after discharge. We use indefinite oral antibiotic therapy as prophylaxis against reinfection (suppression) only in rare circumstances. Postoperative imaging (CT or ultrasound) should be performed out to 1 year to assure resolution of infection at the treated site.

Antibiotic-Loaded Beads

We have used antibiotic-loaded PMMA beads in our wound sterilization algorithm to aid in the treatment of early and late extracavitary prosthetic graft infection.⁷⁶ Beads are made in the operating room with PMMA powder, liquid catalyst, and either vancomycin (1 g), daptomycin (1–1.5 g), tobramycin (1.2 g), or gentamicin (1 g) according to initial culture results. The hardening cement mix is molded into 5-mm beads on stainless steel wire mandrels and implanted in the depth of the wound with temporary skin closure and adjacent closed suction drainage

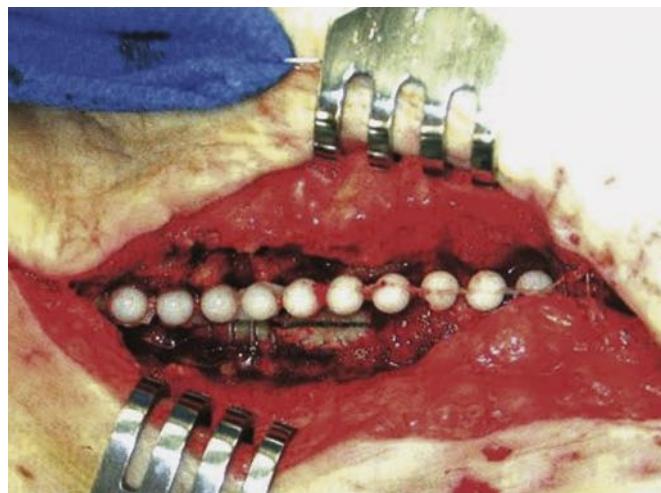


Figure 49.6 Antibiotic-loaded polymethyl methacrylate beads implanted adjacent to an infected polytetrafluoroethylene graft segment and polyester patch. Graft preservation will require further aggressive resection of the skin edges, subcutaneous abscess cavity, and perigraft tissue. (From Stone PA, et al. Use of antibiotic-loaded polymethylmethacrylate beads for the treatment of extra-cavitory prosthetic graft infection. *J Vasc Surg*. 2006;44:757.)

(Fig. 49.6). MRSA was found in 44% of initial cultures in our series. After an average of 2.5 bead replacements (staged debridement/washout/beads every 3–4 days) per patient, culture-proven wound sterilization allowed graft preservation or subsequent *in situ* reconstruction in all cases. Wound healing and avoidance of recurrent infection were achieved in 90% of cases during an average follow-up of 2 years.

Local Tissue Flap Coverage

Transfer or rotation of local soft tissue structures to provide coverage of preserved or new *in situ* grafts may be needed when surrounding tissues are inadequate or an excessive skin defect exists. Pedicles of omentum mobilized within the abdominal or lower thoracic cavity are useful for minimizing recurrence after the treatment of aortic graft infections. Use of sartorius muscle flaps has been the most commonly reported technique for groin wound involvement.⁷⁷ The muscle is typically exposed lateral to the femoral vessels, divided proximally from its iliac spine attachment, and mobilized medially without tension with preservation of as many segmental feeding vessels as possible (Fig. 49.7). Other rotational muscle/fascial flaps can be used for groin wound VSSI adjuncts, including the rectus abdominis, rectus femoris, and gracilis.

We have used sartorius flaps in 21% (89/422) of groin-related, early and late VSSI cases, primarily as part of graft preservation or *in situ* replacement therapies.⁷⁸ Initial graft bed microbiology revealed 65% Gram-positive, 20% Gram-negative, and 15% mixed infections. An attempt was made to sterilize groin wounds with staged debridement and antibiotic-loaded beads to allow delayed application (after a mean 9 days) of sartorius flaps. However, immediate flap construction was required in 10% of patients because of extensive soft tissue loss with exposed graft/repair. Flap application was used in nearly half of the cases where the VSSI was improving clinically after staged debridement with no gross infection/exudate but with residual positive wound culture results. Six (7%) recurrent infections occurred over 4 to 5 years of follow-up. Sartorius flaps



Figure 49.7 Sartorius muscle flap divided superiorly and mobilized toward the upper medial groin wound to cover exposed prosthetic cross-femoral graft after serial debridements of the abscess bed and adjunctive use of polymethyl methacrylate beads loaded with daptomycin plus tobramycin. Skin closure was possible over the sartorius flap, and a bulb-suction drain was placed in the lateral harvested sartorius bed. The patient's head is to the left of photo and the perineum is at the upper edge of the photo.

may not completely eliminate the risk of reinfection for incompletely sterilized graft beds, but muscle coverage can salvage complex groin wounds associated with VSSI.

Endograft Device Infection

The incidence of aortic endograft infection in large institutional experiences has been low (0.1%–1.2%),^{79–81} but isolated case reports have evolved into multi-institutional modest-sized cohorts documented more recently.^{31,35–37,82,83} One-third of abdominal and thoracic aortic endograft infections manifest as aortoenteric or bronchial fistulas, with speculation that residual inflammation results from large intact aneurysms with pulsatility, persistent endoleak, or sac pressurization. Bacteremic or direct seeding may be responsible for endograft infections associated with catheter-based endoleak embolizations.⁸⁴

Definitive treatment of endoprostheses infection after EVAR, similar to open aortic graft infections, has generally been managed by explantation of the device and *ex situ* bypass or *in situ* replacement with SFPV, cryopreserved allografts, or prosthetic graft. The operative mortality risk appears to be significant (10%–30%) for these definitive interventions, with

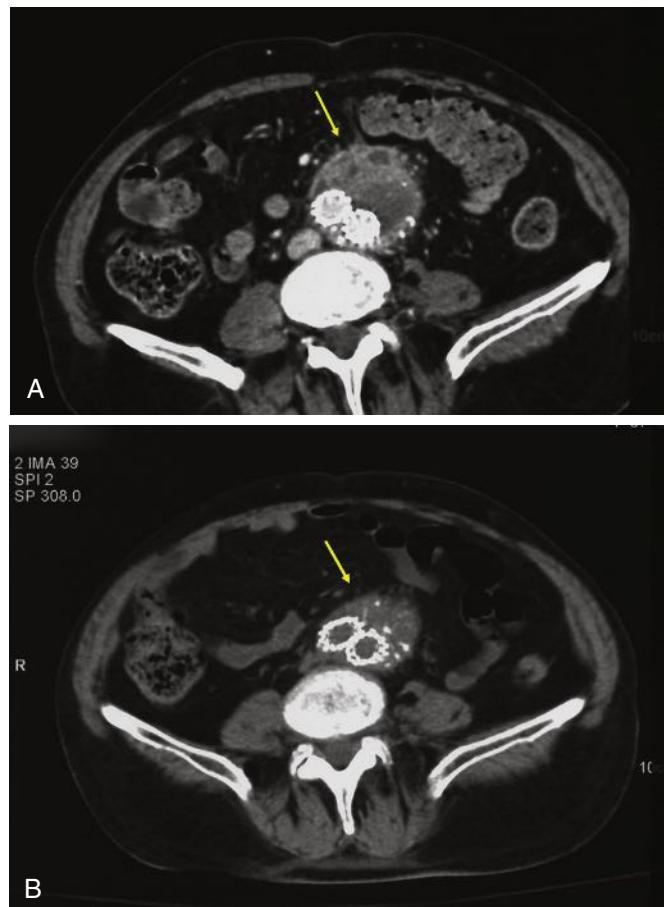
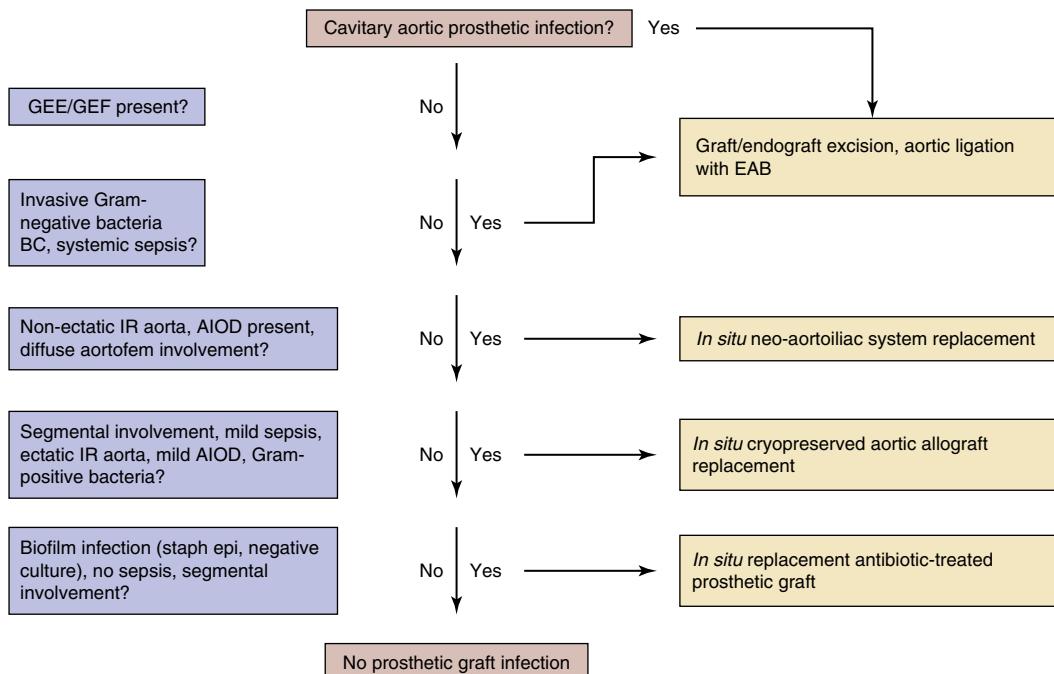


Figure 49.8 Infection associated with an abdominal aortic aneurysm endograft manifested as staphylococcal bacteraemia and back pain. (A) Inflammation in the anterior region of the distal infrarenal sac with patent aortoiliac stent-graft limbs (arrow). (B) Resolved inflammation/infection 16 months later, after a 3-month course of parenteral antibiotics (arrow).

reinfection occurring in 5% to 10% of patients. The largest reported experience of EVAR infection management of Smeds et al.⁸³ documented *in situ* replacement (11% NAIS, 29% CAH, 54% prosthetic) and excision/*ex situ* bypass (6%) repairs and 24% of endograft infections were associated with GEE/GEF. Results comparable to interventions for open aortic prosthetic graft infections were reported including 11% 30-day mortality, 52% 5-year survival, late graft rupture (3%) or reinfection (11%). Shorter patient survival was predicted by no antibiotic-treated *in situ* prosthetic repairs, Gram-negative infections and presenting GEE/GEF.

The potential use of endovascular techniques to treat endograft-related infected pseudoaneurysms or enteric erosions is extrapolated from limited experiences with endograft treatment of mycotic aneurysms or aortoenteric/bronchial fistulas^{85,86} but has shown limited durability and represents only a bridge to definitive open repair.⁸⁷ Several reports have shown successful treatment of endograft infections without device explantation. This approach should be offered only to extremely high-risk patients without aortoenteric erosions who have a rapid, favorable clinical response to parenteral antibiotics (6 weeks minimum duration) (Fig. 49.8). Recurrent or persistent sepsis mandates explantation.

CHAPTER ALGORITHM



Suggested treatment algorithm for infected cavitary aortic prosthetic grafts and endografts (Bunt extent P0 infection). Parameters affecting selection of optimal reconstruction approach included. *EAB*, axillo femoral extra-anatomic bypass; *BC*, blood cultures; *IR*, infrarenal; *AIOD*, aortoiliac occlusive disease.

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Anastomotic Aneurysms

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INTRODUCTION	640
INCIDENCE AND ANATOMIC LOCATION	640
PATHOGENESIS	641
Local Factors	641
Arterial Wall Degeneration	641
Suture Line Disruption	641
Graft Failure	642
Infection and/or Inflammation	642
Technical Errors	642
Mechanical Stress	642
Systemic Factors	644
Prevention	644
CLINICAL DIAGNOSIS	644
HISTORY AND PHYSICAL EXAMINATION	644
Imaging	645

SURGICAL TREATMENT	645
Indications for Treatment	645
Principles of Treatment	646
Open Repair	646
Femoral Anastomosis	646
Aortic Anastomosis	646
Iliac Anastomosis	648
Carotid Anastomosis	648
Endovascular Repair	649
Femoral Anastomosis	649
Aortic Anastomosis	649
Iliac Anastomosis	650
Carotid Anastomosis	650
OUTCOMES	650
CHAPTER ALGORITHM	651

INTRODUCTION

In 1956, Birch et al. reported the first case of anastomotic aneurysm in a patient after prosthetic aortic graft placement.¹ Since then, anastomotic aneurysms have been recognized as an infrequent, although important, late complication of prosthetic arterial reconstruction. Although true native aneurysmal degeneration may occur at an anastomotic site, the majority of anastomotic aneurysms are false because they are composed of a fibrous pseudocapsule rather than the normal component layers of the arterial wall. Notably, anastomotic aneurysms have the potential for significant morbidity and mortality, and they present clinical challenges in their detection, evaluation, and management.

INCIDENCE AND ANATOMIC LOCATION

Overall, anastomotic aneurysms complicate 1% to 4% of arterial anastomoses.^{2–5} The incidence of anastomotic aneurysms, however, is influenced substantially by anatomic location, surgical technique, time from anastomotic construction, integrity of the host artery at the original operation, and other local and

systemic factors. When reporting incidence, anastomotic aneurysm formation may be described by the number of patients, or more accurately, by the number of anastomoses, as a patient with an aortobifemoral bypass, for instance, has one aortic anastomosis and two femoral anastomoses at risk.⁶

The interval to presentation of anastomotic aneurysm has increased.^{7,8} Previously seen as an early phenomenon, anastomotic aneurysms in most modern series present at a mean of 6 years following graft implantation,^{8–13} although associated infection can shorten this interval dramatically.¹⁴ Anastomotic aneurysms after reconstruction for aortoiliac occlusive disease are more likely to have late presentations (16 years vs. 9 years for aneurysmal aortic disease)¹⁵ and are more likely to represent degeneration of the anastomosis rather than true aneurysmal change.¹⁶

The most common anatomic site of anastomotic aneurysm formation is the femoral artery, complicating from 0.5% to 24% of reconstructions. In a large retrospective analysis of anastomotic aneurysms after prosthetic reconstructions for aortoiliac occlusive disease, van den Akker et al.¹⁷ reported an overall incidence per patient of 13% and an incidence per anastomotic site of 4.8%, 6.3%, and 14% for aortic, iliac, and femoral anastomoses respectively. In addition, the cumulative freedom from anastomotic aneurysm formation at 15 years was

92%, 84%, and 76% for aortic, iliac, and femoral sites. This propensity of anastomotic aneurysms to form at the femoral location has been documented by others.^{6,9}

Large retrospective studies of graft-related complications for abdominal aortic aneurysm repair report a cumulative incidence of anastomotic aneurysm of 1.3% to 3.0%.^{18,19} Based on three decades of experience with open repair of extent I to IV thoracoabdominal aortic aneurysms, Latz et al. reported a cumulative incidence of anastomotic aneurysms of 2.6% to 3.0%.^{20,21} The incidence of aortic and iliac anastomotic aneurysms, however, is probably underestimated because of inadequate surveillance, prolonged time to recognition, and their initially quiescent behavior.²² Studies with routine radiologic surveillance estimate the incidence of anastomotic aneurysms of the aorta and iliac arteries to be approximately 10%, and may reach 36% by Kaplan-Meier analysis at 15 years.^{17,23,24}

The documented incidence of anastomotic aneurysms following carotid endarterectomy (with or without patch angioplasty) is much lower, approximately 0.3%.²⁵ However, following repair of extracranial carotid aneurysms, anastomotic aneurysms can complicate 13% to 57% of cases.²⁶ The interval to presentation may occur as early as weeks following carotid intervention, although the majority of reported cases present from 5 to 12 years after reconstruction. With improved operative technique and the introduction of superior prosthetic materials, carotid anastomotic aneurysms are most commonly associated with surgical site infection and, more specifically, prosthetic infection (see Ch. 97, Carotid Artery Aneurysms).²⁷

PATHOGENESIS

An anastomosis between two vascular structures is potentially subject to failure and hence aneurysm formation. Anastomotic aneurysms occur almost exclusively between prosthetic grafts and native arteries, with only rare occurrences in completely autogenous anastomoses. When a suture line between two vascular structures is disrupted, an anastomotic aneurysm may form. The egress of blood from the defect forms a pulsatile hematoma that, while in continuity with the bloodstream, becomes lined peripherally with laminated thrombus that eventually becomes encapsulated by surrounding host tissue. A fibroblastic process that initiates the formation of a tissue capsule ensues. The capsule, essentially a false aneurysm cavity, is subjected to systemic arterial pressure and may gradually enlarge, occasionally resulting in local complications of expansion, distal embolization, or rupture.

Several etiologic factors have been implicated in the pathogenesis of anastomotic aneurysms yet the relative importance ascribed to each factor varies substantially by author or institutional experience. Nonetheless, because anastomotic disruption is pivotal in anastomotic aneurysm formation, the pathogenesis may be conceptualized simplistically by considering local and systemic etiologic factors. Each factor may induce or contribute to anastomotic failure, and each has assumed prominence during various time periods. Because no robust

BOX 50.1		Factors Associated with the Development of Anastomotic Aneurysms
Local		Systemic
<ul style="list-style-type: none"> • Arterial wall degeneration • Suture line disruption • Prosthetic graft failure • Infection/inflammation • Technical errors • Mechanical stress 		<ul style="list-style-type: none"> • Smoking • Hyperlipidemia • Hypertension • Anticoagulation • Systemic vasculitides • Generalized arterial weakness

data exist to corroborate the contribution of some of these factors to the development of anastomotic aneurysms, several factors are accepted on a theoretical basis alone (Box 50.1).

Local Factors

Arterial Wall Degeneration

Degeneration of the host arterial wall is often associated with progression of atherosclerosis, which compromises vessel integrity and impairs a critical component of the vascular anastomosis.^{18,27,28} A consistent operative finding at exploration for anastomotic aneurysm is an intact unit of suture and prosthesis that has nonetheless separated from an attenuated arterial wall. In a cohort of 45 patients with 49 anastomotic aneurysms, Skourtis et al.¹² demonstrated the contribution of host arterial degeneration. After operative treatment, 28 arterial specimens were examined microscopically and demonstrated a reduction or absence of elastic fibers in the media and replacement of smooth muscle cells by acellular fibrous connective tissue. Hyaline degeneration of the media and adventitia was also appreciated. In these instances, however, it can be difficult to differentiate anastomotic false aneurysm development from true aneurysmal degeneration of the native vessel.

Suture Line Disruption

Prosthetic graft anastomosis with a native artery depends indefinitely upon the integrity of the suture line, as no lasting union occurs as it would between two native vessels. Suture material, particularly silk, was recognized as a central factor contributing to anastomotic aneurysm formation in early reports. Silk suture gradually dissolves and is eventually resorbed by phagocytosis and other processes. This discovery culminated in the abandonment of silk suture for vascular anastomosis. Unfortunately, several successors of silk, including polyethylene and nylon, were also implicated in anastomotic aneurysm development, in general because of loss of tensile strength and ultimate suture disruption.²⁸ Monofilament polypropylene (Prolene, Ethicon, Livingston, Scotland) suture was introduced commercially in 1969 and has enjoyed favor among vascular surgeons primarily because of its minimal tissue reactivity, low thrombogenicity, inherent resistance to infection, low coefficient of friction during suturing, and excellent maintenance of tensile strength without biodegradation.²⁹ Despite these advantages, polypropylene suture readily frays and fractures, particularly with instrumentation and indiscriminate

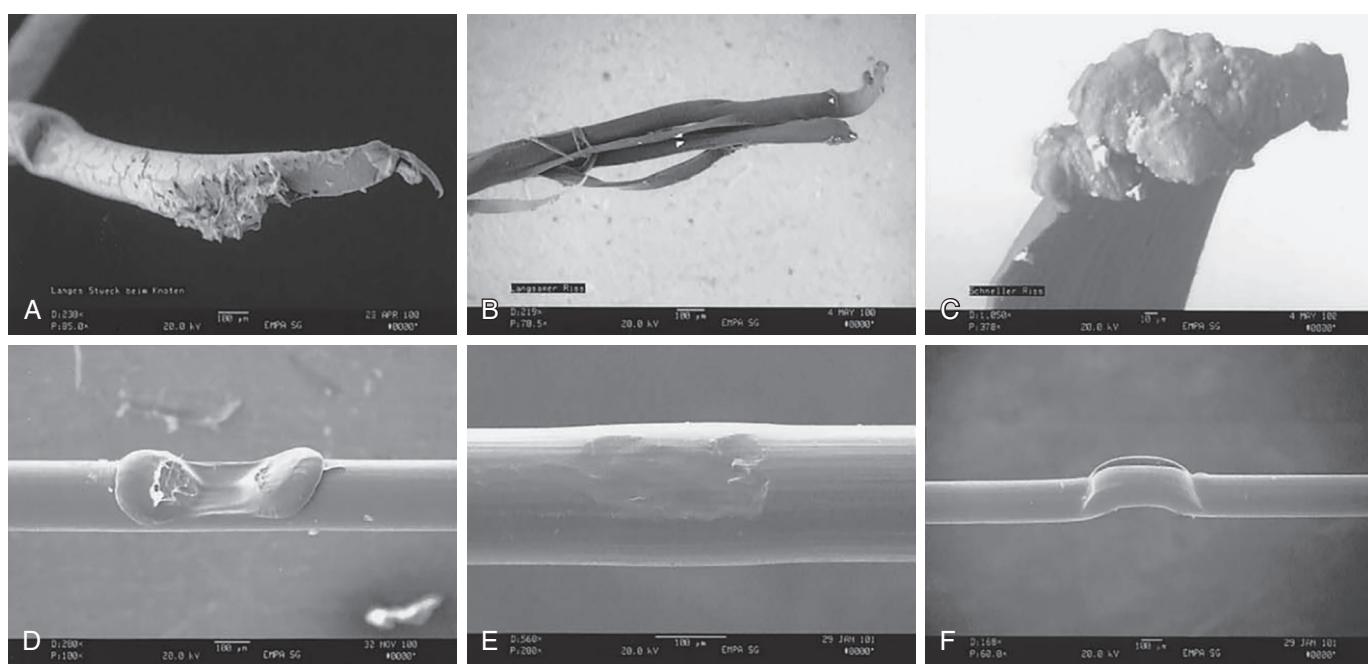


Figure 50.1 Electron Microscopy of Polypropylene Suture. (A) Unexplained suture rupture extracted from an anastomotic aneurysm. (B) Damage from manual slow pulling. (C) Damage from fast pulling. (D) Thermal damage from electrocoagulation with a very short contact time. (E) Damage after soft compression with surgical forceps. (F) Damage after arterial clamp placement. (Reprinted from Huber C, Eckstein FS, Halbeisen M, Carrel TP. Rupture of a polypropylene suture after aortic operation: a scanning electron microscopical assessment of potential mechanisms. *Ann Thorac Surg*. 2003;75(4):1318–1321, with permission from Elsevier.)

handling (Fig. 50.1).³⁰ Polytetrafluoroethylene (PTFE) suture is preferred by some surgeons because of its favorable suturing characteristics and relatively inert behavior in tissues, although its breaking strength is half that of polypropylene.³¹

Nonsuture methods of vascular anastomosis that have recently been explored include rings, staples, clips, cuffs, stents, and adhesives.^{32–36} Purported advantages of nonsuture methods include decreased tissue reactivity, diminished vessel trauma, and technical simplicity and efficiency. Only clips are associated with an acceptable complication profile.³⁷ However, these methods have been reported in only small case series, and before adoption can become widespread, long-term data are needed, especially regarding the incidence of anastomotic aneurysm formation.

Graft Failure

Both early and modern generations of prosthetic grafts have infrequently been incriminated as important factors in anastomotic aneurysm formation. Although knitted and, less commonly, woven polyester grafts dilate over time, they consistently maintain their structural integrity. Notwithstanding, several investigators have associated textile graft dilatation and compliance mismatch between the graft and host artery with development of anastomotic aneurysms. Thus, prosthetic grafts may indirectly contribute to late anastomotic disruption.^{13,38,39} A potential disadvantage of woven polyester grafts is their tendency to fray with handling. However, incorporation of a greater margin of graft into the anastomosis functionally eliminates this feature as a cause of late anastomotic failure (see Ch. 66, Prosthetic Grafts).

Infection and/or Inflammation

Inflammatory states are recognized causes of anastomotic aneurysms, and are frequently the etiology when they occur in the early postoperative period. An inflammatory process may occur in response to implantation of prosthetic materials, postsurgical hematoma or lymphocele, or acquired vasculitides, such as Behcet disease.⁴⁰ Inflammation caused by acute or indolent graft infection may also lead to anastomotic aneurysm formation (Fig. 50.2). Even in the absence of clinical signs of infection, bacterial isolates, especially coagulase-negative staphylococci, have been isolated from as many as 60% to 80% of excised graft material.^{41–43} Although streptococci or staphylococci are the commonly implicated pathogens in graft infections,⁴⁴ anaerobic species such as *Propionibacterium* have also been isolated from anastomotic aneurysms.⁴⁵

Technical Errors

Meticulous attention to suturing, including incorporation of generous portions of the arterial wall, especially in arteries subjected to concurrent endarterectomy, is paramount in preventing eventual anastomotic breakdown. Graft tension during construction of an anastomosis also contributes to late disruption and aneurysm formation. Incorrect suture handling, such as grasping the suture with forceps or clamps, may fracture sutures and predispose an anastomosis to late failure. The use of sutures of adequate strength and size also assists in minimizing technical errors.

Mechanical Stress

Myriad mechanical forces operate at an anastomosis and may differentially contribute to anastomotic aneurysm development.

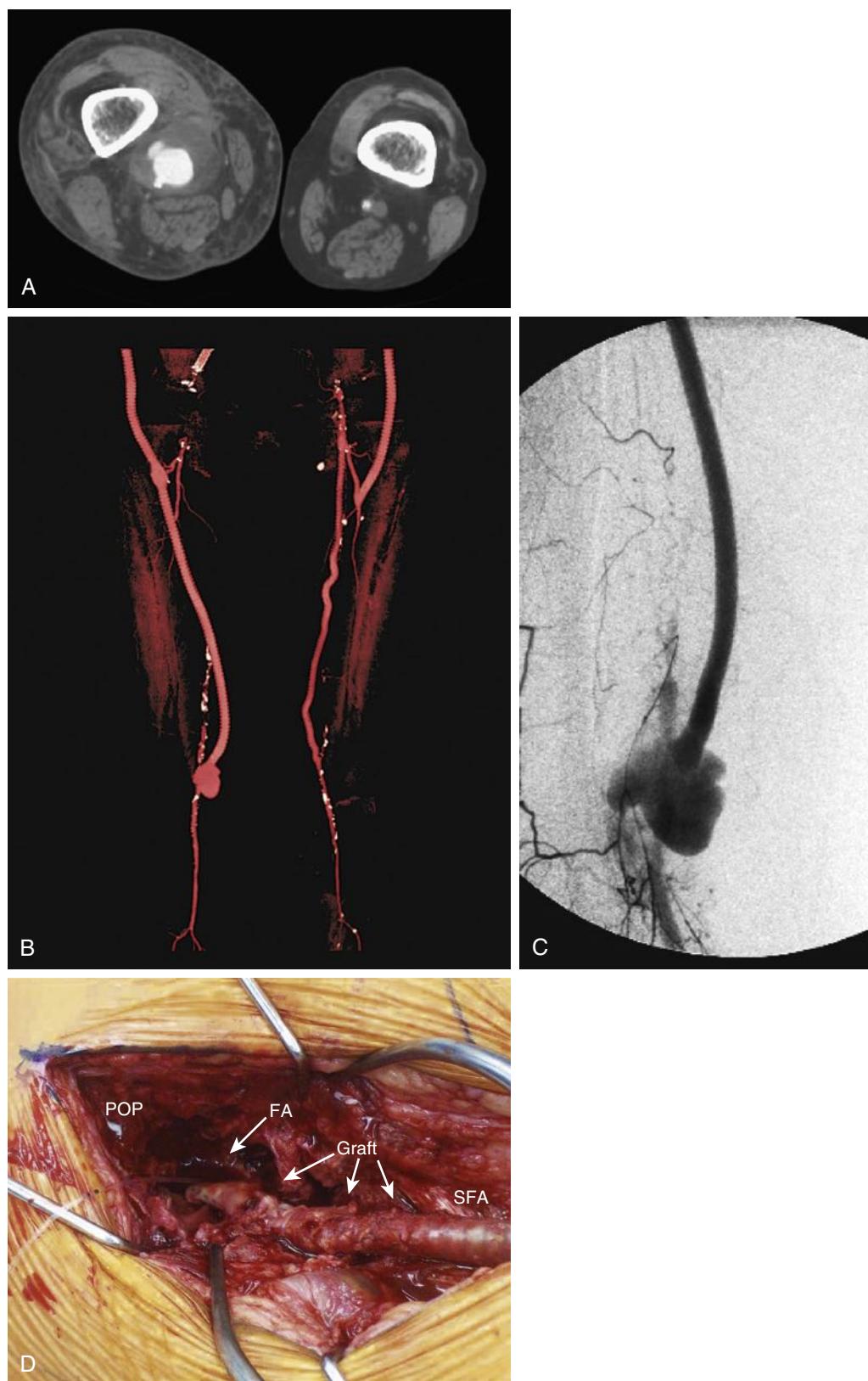


Figure 50.2 Infected Anastomotic Aneurysm Involving the Distal Femoropopliteal Bypass Graft. (A) Axial computed tomographic images from a preoperative angiogram. (B) Reconstructed images from a preoperative computed tomographic angiogram. (C) Intraoperative angiogram demonstrating a false aneurysm. (D) Degenerated polytetrafluoroethylene graft to the popliteal artery (POP) anastomosis. FA, false aneurysm; SFA, superior femoral artery.

Formation of an anastomosis between a prosthetic graft and an artery establishes compliance mismatch. The inherent properties of a prosthetic graft include nondistensibility and a tendency for latent dilatation, both of which impose mechanical or shear stresses on an anastomosis. Laplace's law states that wall tension increases proportionally with radius and pressure. Accordingly, prosthetic dilatation may transmit tension to the suture line and adjacent host artery, resulting in anastomotic disruption. Polytetrafluoroethylene felt strips are commonly used to reinforce aortic anastomoses and prevent disruption.^{46,47} Hosoyama et al. showed a lower rate of anastomotic aneurysms when felt reinforcement was performed using basic fibroblast growth factor incorporated polyglycolic acid felt.⁴⁸ The principles of Laplace's law can also be applied to the diameter of the anastomosis: the greater the diameter, particularly in end-to-side anastomoses, the greater the tension imposed on a suture line.^{38,39} Extraneous tension on the anastomosis may result in elastic recoil of the graft, leading to separation from the vessel wall.

According to laws of fluid mechanics, the larger the incident angle between the graft and recipient artery, the lower the flow rate through the anastomosis and the greater the associated turbulence and shear stress on the suture line. Hence minimizing the angle between the host artery and the graft may impart a hemodynamic benefit and prevent late anastomotic complications. In particular, end-to-end, rather than end-to-side, anastomoses better establish optimal hemodynamic conditions and reduce anastomotic turbulence.⁴⁹

Systemic Factors

Several systemic factors are thought to contribute to anastomotic aneurysm formation. Smoking, hypertension, and hyperlipidemia may facilitate anastomotic failure through local effects on arterial wall integrity. Perioperative systemic anticoagulation occasionally complicates the postoperative course through local wound hematoma, a recognized local etiologic factor in anastomotic aneurysm development. Acquired vasculitides are also associated with anastomotic aneurysm development. Behçet disease, an autoimmune vasculitis, is a multisystem disorder characterized by severe arterial and venous manifestations (see Ch. 138, Vasculitis and Other Arteriopathies). Operative intervention in patients with Behçet disease is complicated by anastomotic aneurysm formation in 30% to 50% of these patients because of chronic vasculitis and arterial wall fragility.^{40,50} Similar manifestations and complications are observed in Takayasu arteritis and in the connective tissue disorder Ehlers–Danlos syndrome type IV (see Ch. 140, Takayasu Arteritis and Ch. 141, Arterial Disease in Patients with Connective Tissue Disorders).⁵¹

Prevention

An understanding of the pathogenesis and risk factors associated with anastomotic aneurysms contributes to their prevention. Deliberate attention to surgical technique is paramount. Anastomoses must be constructed without excessive

tension and by incorporating sufficient graft and arterial wall into the suture line, especially if concurrent endarterectomy is performed. Judicious use of adjunctive endarterectomy is advisable. When feasible, an end-to-end anastomosis should be selected unless preservation of critical vascular beds is required (e.g., retrograde iliac perfusion). If an end-to-side anastomosis is performed, a minimum incident angle should be achieved at the anastomotic site.² In the modern era, the choice of suture and graft material is probably irrelevant and subject to the surgeon's discretion. Nonetheless, it is recommended that the selected prosthesis have a diameter equal to that of the recipient artery. Strict attention to skin preparation and aseptic operative technique is critical, as is preoperative antibiotic administration. Additional prophylactic strategies include meticulously achieving hemostasis, minimizing lymphatic disruption, avoiding adventitial dissection (i.e., ex-arterectomy), and accurate wound closure.^{9,11,49} Despite adherence to the aforementioned principles, anastomotic aneurysms may not be preventable, so periodic surveillance should be conducted to decrease related complications. All patients treated with graft material should undergo long-term evaluation, including clinical examination, color Doppler ultrasound, and if necessary, angiographic computed tomography (CT).

CLINICAL DIAGNOSIS

The diverse clinical manifestations of anastomotic aneurysms are determined largely by anatomic site. Because most anastomotic aneurysms are asymptomatic, they are generally discovered incidentally during routine surveillance or radiologic examinations for unrelated clinical problems.

HISTORY AND PHYSICAL EXAMINATION

A careful, systematic physical examination will detect most femoral and other superficially located anastomotic aneurysms. In clinical practice, an anastomotic aneurysm is detected by examination as a palpable, occasionally tender, pulsatile mass. Thus, periodic clinical evaluation with directed physical examination is recommended indefinitely after construction of prosthetic femoral anastomoses. Over a 15-year period, Demarche et al.⁹ retrospectively described their extensive experience with femoral anastomotic aneurysms. Of 142 anastomotic femoral aneurysms, 64% presented as an asymptomatic pulsatile mass, 19% presented with acute limb ischemia, 9% presented as a painful groin mass, and 7% presented with acute hemorrhage. Two patients (1%) presented with distal microemboli and limb edema, respectively. Overt infection complicated the presentation of 7% of anastomotic aneurysms. The majority of other series reported similar presentations.^{11,13,52} Thrombosis, embolization, and venous or neurogenic compression are also well-documented complications of femoral anastomotic aneurysms.¹⁴

Intraabdominal anastomotic aneurysms may evade clinical detection until they cause symptoms or enlarge sufficiently that they become palpable. Most aortic and iliac anastomotic

aneurysms present as an asymptomatic pulsatile mass or with abdominal or back pain, but they can produce more threatening clinical manifestations such as rupture, infection, distal embolization, erosion with fistulization, or hemorrhage.^{10,12} Occasionally, aortic and iliac anastomotic aneurysms are discovered incidentally during radiologic examinations for unrelated clinical problems. Many large intraabdominal anastomotic aneurysms are palpable on physical examination, particularly in nonobese patients. Small or intracavitory anastomotic aneurysms, however, are often not appreciated by physical examination and require focused radiologic studies for diagnosis. Despite the relatively high incidence of anastomotic aneurysms long-term from the operating room, there are no clear guidelines in place for routine imaging follow-up of patients with aortic and iliac artery anastomoses.

Many carotid anastomotic aneurysms display progressive asymptomatic enlargement, which is rarely appreciated on physical exam. However, local compression, distal embolization, neurologic symptoms, and even rupture are notable manifestations. Rupture is fortunately infrequent but may occur in approximately 3% of cases.²⁶

Imaging

During surveillance or when an anastomotic aneurysm is suspected but cannot be confirmed by examination, ultrasonography, computed tomographic arteriography (CTA), and magnetic resonance arteriography (MRA) are reliable diagnostic modalities. The quality and resolution of modern CTA and MRA often obviate the need for conventional catheter-based arteriography (Fig. 50.3). Moreover, conventional arteriography often cannot identify or provide size information for anastomotic aneurysms because the true diameter is obscured by thrombus.^{53,54} To determine the validity of several current vascular imaging modalities in diagnosing aortic anastomotic aneurysms, Bastounis et al.⁵⁵ performed a cross-sectional study comparing B-mode ultrasonography, CT, magnetic resonance imaging (MRI), and digital subtraction angiography (DSA). Defining color-coded Doppler imaging as the gold standard, they determined that all modalities had sensitivities of 100%, but only MRI, DSA, and enhanced CT possessed sufficient specificity, and only MRI possessed sufficient positive predictive value for diagnostic utility. Although interesting, this study's applicability is limited by the small number of anastomotic aneurysms encountered and by modern technologic improvements in CT and MRI scanners.

The discovery of an anastomotic aneurysm at one site, particularly if femoral, necessitates definitive radiologic evaluation of the remaining anastomoses, because synchronous anastomotic aneurysms are often detected and may occur in up to 36% of patients.¹⁷ Similarly, 13% of patients with abdominal anastomotic aneurysms concurrently harbor femoral anastomotic aneurysms.⁵⁶

When an infected anastomotic aneurysm is suspected, non-specific serum markers such as erythrocyte sedimentation rate and C-reactive protein levels may suggest a systemic inflammatory state. A technetium-labeled white blood cell scan may also

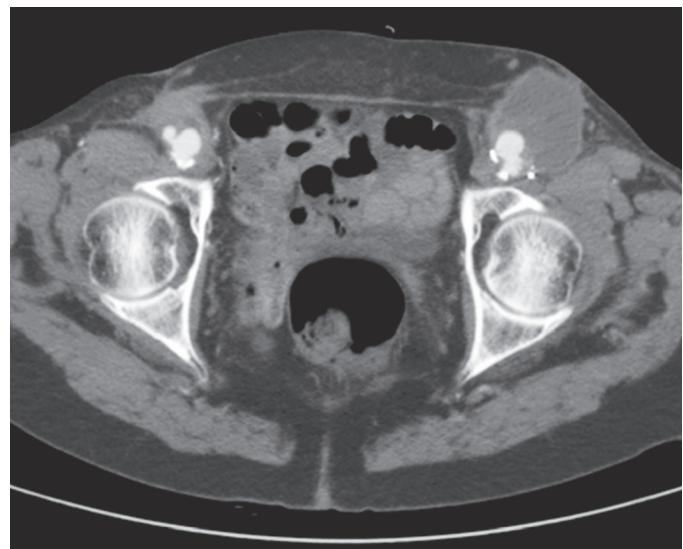


Figure 50.3 Axial computed tomographic image of bilateral femoral anastomotic aneurysm after aortobifemoral bypass.

assist in determining the probability of an infected anastomotic aneurysm.⁵⁷

SURGICAL TREATMENT

Indications for Treatment

The indications for intervention when an anastomotic aneurysm is detected depend on several interrelated variables, including size, location, symptom status, and suspected etiology. Most believe that femoral anastomotic aneurysms may be safely observed until they achieve a diameter of 2 to 2.5 cm, or until they produce symptoms due to local expansion or distal embolization.⁵⁸ While data on rupture risk as a function of size are not available, it is generally accepted that this probability increases as they grow larger.⁵⁹ Early appearance of an anastomotic aneurysm often signals a more ominous etiology and frequently requires additional evaluation and earlier intervention. Urgent treatment is required for severe manifestations of anastomotic aneurysms, such as hemorrhage, graft thrombosis, and embolization.

Although less common, aortic and iliac anastomotic aneurysms should be considered for repair at discovery because of difficulties in surveillance and the seriousness of their potential complications.^{3,23,24,60} However, some authors recommend selective intervention for aortic and iliac anastomotic aneurysms.^{15,54} The decision for repair should be based on assessment of operative risk, and those who do not undergo immediate repair should undergo periodic clinical and radiologic surveillance. Saccular aortic and iliac anastomotic aneurysms represent a special population that historically behave more aggressively and thus may not be amenable to extended surveillance.⁵³

Carotid anastomotic aneurysms are rarely encountered in clinical practice but deserve special attention. The morbidity and mortality attributable to these lesions obligate

consideration for surgical intervention.^{26,61} When infection is suspected or clinically apparent, expeditious intervention is warranted.

Principles of Treatment

Each anastomotic aneurysm should be approached after considering its etiology and how this factor influences its management. Infection should be presumed until definitively excluded by exploration and standard microbiologic techniques. The management of infected anastomotic aneurysms, suggested by perigraft fluid or poor tissue incorporation, often requires complex reconstruction and is associated with increased morbidity and mortality, especially under urgent circumstances.^{14,60}

If using an open technique for repair, operative goals include safely obtaining proximal and distal vascular control, careful preservation of important arterial branches and collateral vessels, and replacement or exclusion of the aneurysm to prevent or limit complications. Tedious and hazardous dissection, often in a densely scarred, altered surgical field, is characteristic of such therapeutic endeavors. Care and judgment is required to prevent premature aneurysm disruption that may result in significant hemorrhage. Excessive mobilization should also be avoided to prevent dislodgement and distal embolization of mural thrombus. In particularly difficult dissections, intraluminal balloon occlusion may assist in controlling inflow or outflow arteries and circumvent an otherwise perilous situation.

Although open surgical techniques have predominated in the literature concerning management of anastomotic aneurysms, several authors have published reports of successful endovascular treatment. Endovascular techniques are particularly suitable for treatment of aortic and iliac anastomotic aneurysms, especially with the advent of fenestrated and branched endovascular devices, and in many circumstances, they have supplanted conventional treatment strategies^{62–79} (Table 50.1; see Ch. 82: Fenestrated and Branched Endograft Treatment of Juxtarenal, Paravisceral, Thoracoabdominal, and Aortic Arch Aneurysms). An algorithm guiding management of anastomotic aneurysms is presented.

Open Repair

When suture disruption is the apparent etiology, especially when anastomotic failure occurs early, simple repair of the anastomosis is an option. However, when arterial wall degeneration, or less commonly, graft deterioration is discovered, insertion of an interposition graft is preferred; this technique is associated with excellent patency and low risk of recurrence.

Femoral Anastomosis

Detailed preoperative arteriography assists in operative planning and provides critical information by documenting the patency and location of the involved arteries, the status of the pelvic circulation, and the likelihood of infection. The existing graft is identified through the previous incision and controlled

for later occlusion (Fig. 50.4). Large femoral anastomotic aneurysms may necessitate proximal control through a supranguinal incision. In this approach, an incision is made between the anterior superior iliac spine and a point halfway between the pubis and the umbilicus. The abdominal wall muscles are divided, and the preperitoneal plane is identified. Exposure is carried posteriorly using blunt dissection. The external iliac artery is identified in association with the vein. Circumferential dissection of the artery allows for loop control or clamping. Alternatively, it is often convenient to employ balloon occlusion of the external iliac artery after dissecting the false aneurysm in the groin. Distal control is next secured by careful dissection of the superficial and deep femoral arteries and other important collateral branches. Balloon occlusion may also be used for any branches that are obscured by dense scar tissue, including the profunda femoris artery.

Following systemic anticoagulation, inflow and outflow arteries are occluded atraumatically, and the anastomotic aneurysm is entered. Local signs of infection, such as purulence, perigraft fluid, and poor graft incorporation, are sought. In the absence of overt infection, a tissue or graft specimen is submitted for microbiologic analysis. If the etiology appears noninfectious, interposition graft replacement is performed. If overt infection is present, an extraanatomic reconstruction may be warranted.

The false aneurysm including the distal graft and degenerative native arterial wall is debrided, and an interposition graft of a diameter similar to that of the recipient artery is selected. Some authors prefer polytetrafluoroethylene in their choice of conduit because of its reduced propensity for dilatation, potentially reducing the incidence of late anastomotic aneurysm recurrence. When permissible, an end-to-end anastomotic configuration is recommended. However, if an end-to-end anastomosis compromises flow to critical vascular beds, such as the pelvic circulation, an end-to-side anastomosis is constructed with care to maintain a minimal incident angle between the graft and host artery. When managing a large false aneurysm, vascularized soft tissue coverage can be achieved with rotational muscle flaps. Several authors strongly advocate similar management techniques.^{14,80,81}

Aortic Anastomosis

Preoperative imaging with noninvasive radiologic studies provides vital information regarding signs of graft infection, selection of a proximal clamp location, aneurysm proximity to visceral branches (especially the renal arteries), and the location of retroperitoneal and intraperitoneal structures (Fig. 50.5). Operative approaches vary by surgeon experience and preference, but both retroperitoneal and transperitoneal approaches have distinct advantages and disadvantages. Frequently, a suprarenal clamp location may be necessary if the anastomotic aneurysm is juxtarenal, and proximal control may be more safely obtained, especially in the presence of scar tissue, via a retroperitoneal approach, especially if it helps avoid the previous operative field.

When open repair is contemplated, most frequently an aortoaortic bypass is performed with a tubular prosthesis that originates from the proximal normal, nonaneurysmal aorta

TABLE 50.1 Endovascular Management of Anastomotic Aneurysms

Series	Year	No. of Patients	Location	Technique	Infected	RESULTS (%)					Mean Follow-Up (months)
						Technical Success (%)	Major Complications (%)	30-Day Mortality (%)	Patency (%)		
Adam et al. ⁶²	2005	3	A	Fenestrated and branched	No	100	33	0	100	12	
Beck et al. ⁶³	2009	18	A	Fenestrated and branched	No	94	11	0	95	23	
Ten Bosch et al. ⁶⁴	2011	58	A/I	Covered stent	No	95	13	2	74.1	41	
Curti et al. ⁶⁵	2001	11	I	Covered stent	Yes	100	0	0	100	28	
Derom and Nout ⁶⁶	2005	7	F	Covered stent	No	100	0	0	100	18.6	
Di Tommaso et al. ⁶⁷	2007	6	A	Covered stent	No	100	0	0	100	26.1	
Faries et al. ⁶⁸	2003	33	A/I	Covered stent	No	100	11	0	—	—	
Gallitto et al. ⁶⁹	2016	20	A	Fenestrated and branched	No	95	25	0	98.7	15	
Gawenda et al. ²²	2003	10	A/I	Covered stent	No	100	0	10	100	—	
Lagana et al. ⁷⁰	2007	30	A/I	Covered stent	No	100	0	3	91	19.7	
Magnan et al. ⁷¹	2003	10	A	Covered stent	No	100	10	0	90	17.7	
Mitchell et al. ⁷²	2007	10	A/I	Covered stent	No	100	10	0	—	—	
Piffaretti et al. ⁷³	2007	22	A/I	Covered stent	No	100	5	0	96	16	
Reyes et al. ⁷⁴	2016	34	A	Fenestrated, branched, and chimney	No	97	18	3	98	23.2	
Sachdev et al. ¹⁵	2007	65	A/I	Covered stent	Yes	98	9	3.80	94	18.1	
Tsang et al. ⁷⁵	2009	11	A/I	Covered stent	No	100	4	0	—	—	
van Herwaarden et al. ⁷⁶	2004	8	A/I	Covered stent	No	100	20	0	88	12	
Wu et al. ⁷⁷	2016	24	A	Covered stent	No	100	21	0	0	43	
Yuan et al. ⁷⁸	1997	12	A/I	Covered stent	No	100	17	0	100	16	
Ziegler et al. ⁷⁹	2007	9	A	Fenestrated and branched	No	100	3	0	—	12	

A, aortic; F, femoral; I, iliac.

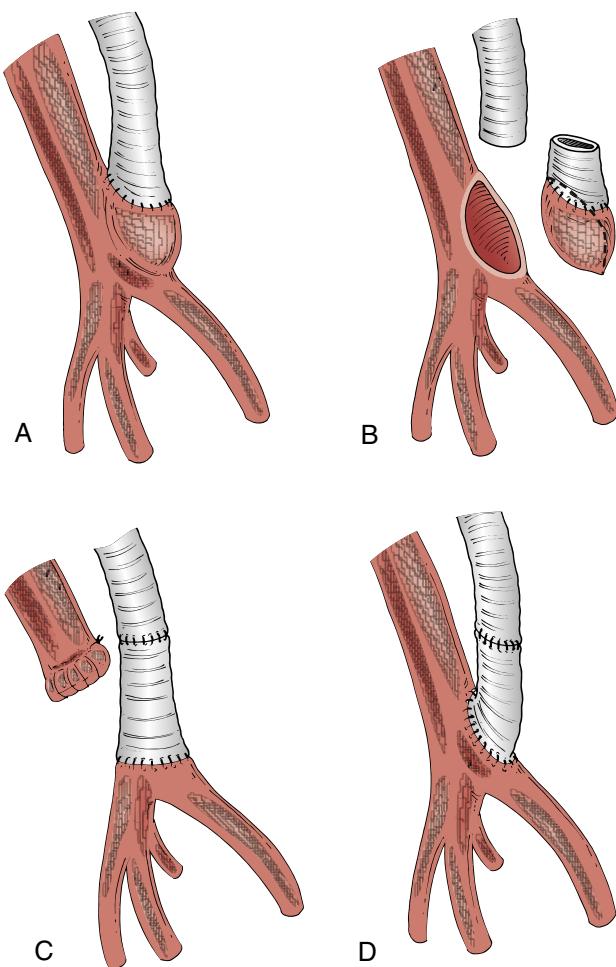


Figure 50.4 (A) Depiction of a femoral anastomotic aneurysm with arterial wall degeneration. (B) View of the femoral anastomotic aneurysm after excision of the false aneurysm. (C) Repair of the femoral anastomotic aneurysm with an interposition graft (end-to-end anastomosis). (D) Repair of the femoral anastomotic aneurysm with an interposition graft (end-to-side anastomosis).

to the existing graft distally. Occasionally, visceral branch bypass is required to ensure a secure proximal anastomosis. Less frequently, and if distal anastomotic revision is required concurrently, implantation of a bifurcated graft (aortobiiliac or aortobifemoral) is expeditious.⁸² If an infectious etiology is discovered intraoperatively, graft excision with extraanatomic bypass or autogenous *in situ* reconstruction is performed. In cases of infected aortic grafts involving the visceral or renal branches, direct reconstruction with nonautologous conduit may be unavoidable.

Iliac Anastomosis

As with aortic anastomotic aneurysms, intervention for iliac anastomotic aneurysms relies on accurate, high-quality non-invasive imaging for operative planning. Often the aneurysm involves the distal anastomosis of a bifurcated prosthesis and is located at or close to the iliac bifurcation. A retroperitoneal (flank) approach provides adequate exposure. Operative principles parallel those employed at aortic locations. Preservation of the internal iliac artery often complicates reconstruction, but may be accomplished with a separate bypass. The ureter should be carefully identified and protected, especially when managing large or inflammatory anastomotic aneurysms. Methods of ureteral protection include identification of the ureter in proximal unaltered tissue planes and preoperative placement of a ureteral stent.

Carotid Anastomosis

Based on clinical experience with primary carotid artery aneurysms, anastomotic aneurysm management using nonoperative strategies is thought to yield excessive morbidity and mortality.⁸³ Traditional management of carotid anastomotic aneurysms depends largely on the clinical suspicion or subsequent intraoperative discovery of infection, especially when a prosthetic patch is present. The preferred method of reconstruction

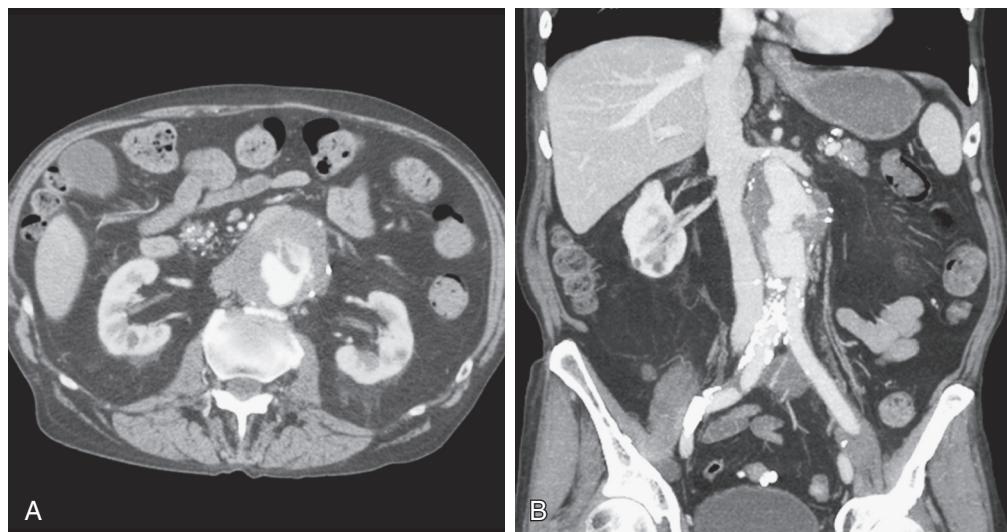


Figure 50.5 Proximal Aortic Anastomotic Aneurysm After Aortobifemoral Bypass. (A) Axial view. (B) Coronal view.

is resection of the aneurysm with interposition bypass grafting or repair with patch angioplasty. Resection with primary anastomosis, extracranial to intracranial carotid bypass, and carotid ligation have also been described.²⁵ When infection is the presumed etiology, reconstruction with the saphenous vein is indicated. Carotid ligation has generally been limited to use in failed reconstruction attempts, and has been associated with a mortality rate of 28% to 50%.^{25,83,84}

Endovascular Repair

Femoral Anastomosis

Open operation represents the traditional management strategy for femoral anastomotic aneurysms. Endovascular repair of anastomotic aneurysms at this location is problematic because of chronic hip motion that may cause deformation, fracture, or migration of implanted stents. Successful endovascular management of ruptured and nonruptured femoral anastomotic aneurysms, however, has been reported in cases of prohibitive operative risk.^{84,85}

Aortic Anastomosis

Conventional open repair of aortic anastomotic aneurysms is formidable and is associated with mortality rates of 3% to 17%.^{23,76} By avoiding the risks of re-operative aortic exposure and suprarenal aortic clamping, endovascular repair presents an attractive therapeutic alternative. Endovascular exclusion of aortic anastomotic aneurysms has been successfully described with both homemade and commercially manufactured stent-grafts, including tubular, bifurcated, and aortic uni-iliac stent-graft configurations.^{15,70,76,86,87} Additionally, fenestrated, branched, and chimney devices are being increasingly used for proximal aortic anastomotic aneurysms involving the visceral vessels.^{62–64,69,74,79,88–90} Stent-graft repair of ruptured anastomotic aneurysms is equally efficacious and advantageous.⁷⁹

Important considerations include the ability to obtain detailed and high-definition CTA with multiplanar reconstructions for precise aortic measurement and graft selection. Particular attention is directed toward the proximal neck to ensure that adequate conditions exist for successful sealing. Neck diameter and length from the lowest renal artery to the flow divider of the existing graft are critical factors. A segment of nonaneurysmal aorta adjacent to the anastomotic aneurysm (the “neck”) is vital to allow endograft fixation and aneurysm exclusion. The availability of a suitable neck is often the limiting factor in this form of therapy. Suprarenal fixation may provide additional proximal stability without an adverse effect on renal function.⁷⁹ Several investigators have noted late complications of endoleak and rupture when tubular endografts are employed because of insecure fixation to polyester graft and exclusive reliance on radial force.¹⁹ However, sufficient graft oversizing (10%–20%) should permit secure sealing.⁷⁹

When the distance from the lowest renal artery to the flow divider is insufficient to permit deployment of a modular bifurcated endograft, an aortic uni-iliac graft may be inserted with adjunctive femorofemoral bypass. As with endovascular repair of *de novo* aortoiliac aneurysms, internal iliac artery occlusion

is occasionally necessary to achieve distal fixation without endoleak.^{76,79} To avoid the risks of buttock claudication, pelvic ischemia, and rarely spinal cord ischemia, pelvic collateral circulation must be carefully investigated. Efforts to preserve at least one internal iliac artery are prudent.⁶³ When intentional internal iliac artery occlusion is planned, proximal embolization is recommended to prevent interruption of important collateral branches.

Increasing use of fenestrated and branched endovascular stent-grafts for the repair of proximal aortic anastomotic aneurysms has been reported, especially in cases where the length or quality of the proximal neck is insufficient.^{62,90} Beck et al. described 18 patients with previous aortic reconstruction who developed juxtarenal aortic aneurysms from 2004 to 2008.⁶³ Technically successful treatment with fenestrated and branched endovascular stent-grafts occurred in all cases, and perioperative complications, including congestive heart failure and myocardial infarction, only occurred in two patients. Thirty-day and 1-year mortality were 0% and 11%, respectively. Mean follow-up was 23 months, with a cumulative primary patency at 95%. Zeigler et al. retrospectively reviewed their experience with the use of fenestrated and branched grafts for para-anastomotic aortic aneurysm repair in patients who were considered high risk for open surgical repair.⁷⁹ Of the nine patients who received fenestrated endoprostheses, technical success was achieved in all. Transient kidney injury was seen in three patients, and permanent renal impairment was seen in one. More recently, Reyes et al. reported on a series of 34 patients undergoing endovascular repair for pararenal aneurysms after prior open abdominal aortic repair.⁷⁴ While the majority of patients underwent fenestrated or branched graft repair, four patients underwent chimney-EVAR. The technical success rate was 97%, with a 3% 30-day mortality. During follow-up, six patients (18%) underwent reintervention, although primary patency of the target aortic branches was 98%. While short- and mid-term outcomes of fenestrated and branched EVAR are promising, long-term outcomes are still largely unknown. Furthermore, specific complications from using these complex techniques, such as target vessel occlusion and type III endoleaks at the side branch joints should be considered during the initial perioperative period and throughout follow-up.

In complicated cases in which the anastomotic aneurysm encroaches on adjacent branches, such as the renal arteries, superior mesenteric artery or celiac trunk, an alternative to a completely endovascular fenestrated or branched repair is a hybrid repair.^{89,91,92} In a review of their experience with complicated pararenal and thoracoabdominal aortic pathologies treated with hybrid approaches, Böckler et al. described two para-anastomotic aneurysms treated with commercially available endografts after open revascularization of visceral and renal arteries.⁹¹ In the descending thoracic aorta, when large anastomotic aneurysms involve the left subclavian artery, a hybrid approach of extra-anatomic revascularization followed by TEVAR can be an alternative. Recently, Aziz et al.⁹² described their experience with a large anastomotic aneurysm in the descending thoracic aorta, at the site of previous repair for coarctation, extending into the left subclavian artery. This was

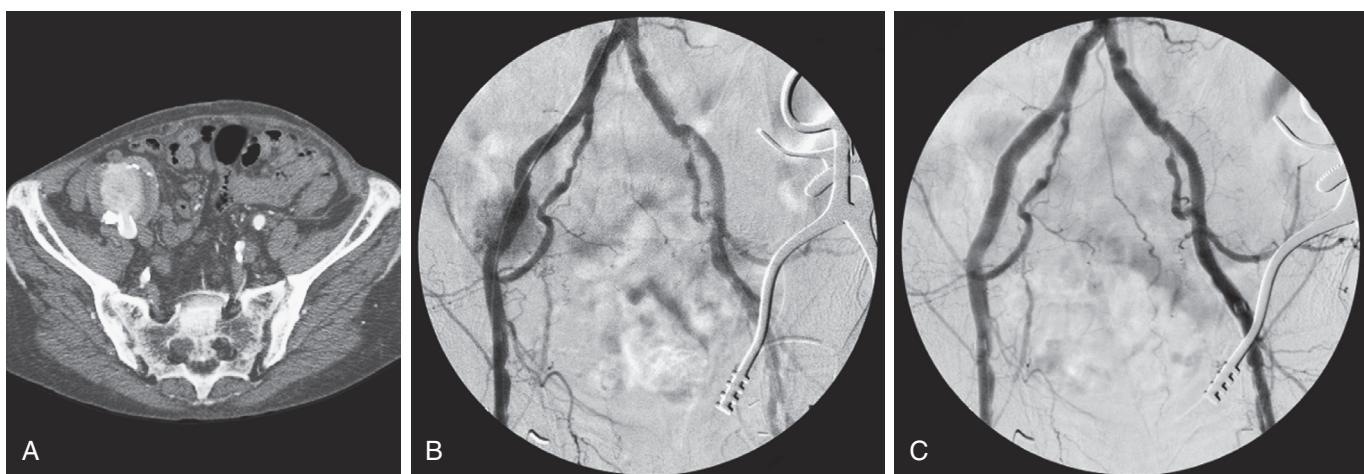


Figure 50.6 (A) Axial computed tomography of a right external iliac anastomotic aneurysm. (B) Diagnostic arteriogram demonstrating a right external iliac anastomotic aneurysm. (C) Successful exclusion of the external iliac anastomotic aneurysm with a covered stent.

repaired using a three-stage hybrid approach involving left carotid to subclavian bypass followed by TEVAR and lastly, coil embolization of the left subclavian aneurysm from a brachial approach.

Concurrent infection should generally be excluded before committing to an endovascular repair strategy, a decision that relies on clinical and radiologic data. When an aortoenteric fistula is present, stent-graft repair may function as a bridge until definitive therapy can be accomplished. If endovascular repair is performed as definitive therapy, it should be used in conjunction with extended antibiotic treatment with possible lifelong antibiotic prophylaxis (see Ch. 51, Local Complications: Aortoenteric Fistula).^{16,63,93}

Isolated reports also chronicle the management of both aortic and iliac anastomotic aneurysms with percutaneous embolization using traditional coils, *n*-butyl cyanoacrylate, and Amplatzer (AGA Medical Corp., Plymouth, MN) atrial septal defect occluder devices.^{94–96} Badran et al. reported a case of embolization with transcatheter delivery of thrombin to a thoracic aortic pseudoaneurysm at the anastomosis between graft and native aorta patch.⁹⁷ It is important to note that the neck of this pseudoaneurysm was narrow, and catheter placement actually occluded the neck, which allowed for successful intervention, emphasizing that practice must be tailored to well-suited cases.

Iliac Anastomosis

Open repair of iliac anastomotic aneurysms is also technically challenging and is associated with significantly higher morbidity and mortality than primary iliac aneurysm reconstruction.^{98,99} Endovascular treatment principles are similar to those employed in the management of aortic anastomotic aneurysms, and successful intervention has been described (Fig. 50.6).¹⁰⁰ Management is frequently complicated by a patent internal iliac artery that requires embolization and coverage for successful aneurysm exclusion.¹⁰¹ However, when preservation of the artery is necessary, separate revascularization with bypass is a durable solution. Hybrid techniques combining open and

endovascular repairs have been successfully used in both symptomatic and ruptured iliac aneurysms.^{102,103}

Carotid Anastomosis

Endovascular techniques recently have been adapted to the management of carotid anastomotic aneurysms. To avoid a difficult dissection and ameliorate the risk of cranial nerve injury, a few investigators have reported successful management of extracranial carotid aneurysms with stent-grafts, endovascular balloon occlusion, and bare-metal stents with adjunctive coil embolization. Zhou et al. reported their experience with the endovascular treatment of 14 carotid anastomotic aneurysms over a 10-year interval.²⁶ Length of hospital stay, cranial nerve injury, and 30-day mortality and stroke rates were significantly lower than those in patients managed with conventional open reconstruction during earlier and concurrent periods. Primary patency of endovascular intervention appears acceptable during early and intermediate follow-up,¹⁰⁴ and no progression of neurologic symptoms has been reported.¹⁰⁵ However, long-term results are currently unavailable.

OUTCOMES

Compared with treatment of *de novo* arterial aneurysms, therapy for anastomotic aneurysms is associated with greater morbidity and mortality primarily because of challenges associated with remedial intervention and advanced medical illness in elderly populations. Mulder et al., in a retrospective analysis of 220 noninfected anastomotic aortic aneurysms managed surgically, reported overall intraoperative mortality rates of 4.5% and 24% in elective and emergency circumstances, respectively.⁶⁰ Similarly, open repair involved an overall morbidity rate of 53% (50% in elective and 70% in emergency operations), with a 14% rate of re-intervention and a 2.6% amputation rate.

As with *de novo* aneurysms, the mortality rate associated with ruptured aortic anastomotic aneurysms is dismal, estimated at 67% to 100%.^{54,60} The discrepancy in mortality and morbidity between elective and emergency repair of

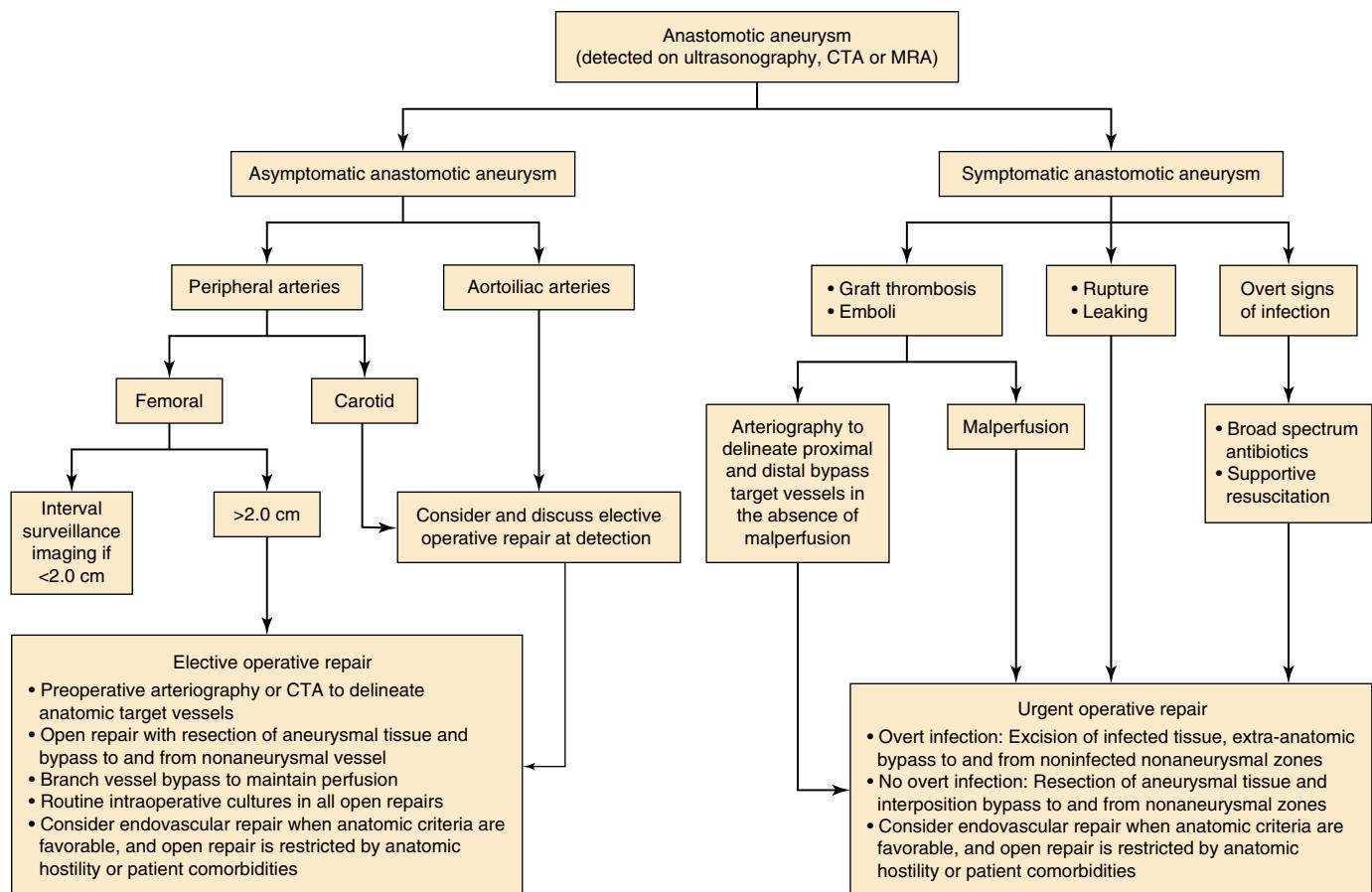
anastomotic aneurysms highlights the argument for early elective repair. For example, Bianchi et al. found 31 treated anastomotic aneurysms in their single institution review over a 25-year period.¹⁰⁶ The mortality rates among the elective and emergency cases were 5% and 66.6%, respectively, and the morbidity rates were 57.8% and 75%, respectively. In addition, the survival rate during follow-up was significantly higher for elective than emergency cases. While elective repair of anastomotic aneurysms carries a higher operative risk than the initial grafting procedure, it appears to be acceptable when compared with the risk of emergency repair following rupture.

Endovascular repair of aortic and iliac anastomotic aneurysms is associated with high technical success and reduced early- and intermediate-term morbidity and mortality compared with open repair. At intermediate follow-up, aneurysm exclusion is consistently observed without a significant incidence of endoleak or conversion to open repair.⁷⁹ Ten Bosch et al. demonstrated the durability of endovascular repair of

anastomotic aneurysms after previous open aortoiliac reconstruction.⁶⁴ The retrospective review of four centers' experience with anastomotic aneurysms in 80 aortic and iliac anastomoses demonstrated high technical success rates and acceptable mortality and morbidity. Exclusion was successfully maintained in 86% of the anastomotic aneurysms over a mean follow-up of 41 months (range 0–106 months).

With modern techniques – namely, interposition grafting – recurrence rates after repair of femoral anastomotic aneurysms have improved.^{11,89,107} Recurrences after initial operative repair occurred in 9.5% to 19% of patients.^{60,108} The risk of recurrence increased with graft dilation and continued arterial wall degradation, as well as with local wound complications and female sex.^{4,109} Compared with the primary operation, repair of femoral anastomotic aneurysms was associated with increased morbidity, including a significant incidence of perioperative hemorrhage and wound infection.¹¹⁰ The effect of different repair techniques on postoperative complication rates has not been reported.

CHAPTER ALGORITHM



An algorithm guiding management of anastomotic aneurysms. *CTA*, computed tomography angiogram; *MRA*, magnetic resonance angiogram.

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A complete reference list can be found online at www.expertconsult.com.

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Local Complications: Aortoenteric Fistula

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INTRODUCTION	653
PRIMARY AORTOENTERIC FISTULA	653
Incidence, Etiology, and Pathogenesis	653
SECONDARY AORTOENTERIC FISTULA	654
Incidence, Etiology, and Pathogenesis	654
Pathogenesis	655
Infection	655
Pulsatile Pressure	655
Technical Error	655
AORTOENTERIC FISTULA AFTER ENDOVASCULAR REPAIR	655
CLINICAL PRESENTATION	656
DIAGNOSIS	656
Computed Tomography	656
Esophagogastroduodenoscopy	656

Angiography	657
Other Tests	657
TREATMENT	658
Urgent Surgical Control of Hemorrhage	658
Management of the Gastrointestinal Defect	658
Surgical Treatment in Stable Patients	658
Primary Aortoenteric Fistula	658
Secondary Aortoenteric Fistula	659
Graft Excision Without Replacement	659
Extra-Anatomic Revascularization	659
In Situ Aortic Graft Replacement	660
Neo-Aortoiliac System Procedure	660
Endovascular Repair	661
RESULTS AND CONCLUSIONS	661
CHAPTER ALGORITHM	662

INTRODUCTION

Aortoenteric fistula (AEF) is defined as a communication between the aorta and gastrointestinal (GI) tract. AEF is classified as primary or secondary based on the underlying cause leading to the fistula development. Primary AEF is a communication between the native aorta and GI tract; secondary AEF is a communication between a reconstructed aorta (for either aneurysmal or occlusive disease) and the GI tract.

Sir Astley Cooper was the first to describe a primary AEF in a publication in 1829. He referred to it as a “sometimes but serious complication of an aneurysmal aorta.”¹ Brock published the first report of a secondary AEF in 1953, wherein he described a fistula between the proximal anastomosis of an aortic homograft and the duodenum.² Heberer performed the first repair of a primary AEF in 1954 by primary closure,³ and MacKenzie et al.⁴ performed the first successful repair of a secondary AEF in 1958.

AEF presents a particularly complicated challenge for the vascular surgeon. When it is left untreated, the outcome is almost universally fatal. However, surgical repair is fraught with complications, and despite continued advances in medicine and critical care, morbidity and mortality rates remain high.

In addition to the difficulties encountered with surgical treatment, AEF is notoriously difficult to diagnose, and as such, a high index of suspicion is required in approaching any patient with GI hemorrhage and history of aortic disease. This chapter reviews the pathogenesis, etiology, diagnostic methods, and treatment options for AEF.

PRIMARY AORTOENTERIC FISTULA

Incidence, Etiology, and Pathogenesis

The incidence of primary AEF has been reported at 0.04% to 0.07% in large autopsy series.⁵ The body of literature available on the subject of primary AEF is small, with approximately 251 cases available in the published literature. Despite the rarity of primary AEF in the population overall, the incidence in patients with aneurysms of the abdominal aorta is 0.69% to 2.36%.⁶ In the majority of cases (83%), an aneurysmal aorta is associated with primary AEF; foreign bodies, tumors, radiotherapy, infection (historically due to tuberculosis and syphilis, but now most commonly caused by *Klebsiella* and *Salmonella*),

and GI tract disease (peptic ulcer disease and perforating biliary stones) account for the remainder of AEF. The mean diameter of the aorta with primary AEF is 6.2 cm; the mean age of patients is 64 years, with a male-to-female ratio of 3:1.⁷

The most commonly described GI tract location for primary AEF is the third and fourth portion of the duodenum (54%). It is presumed that this is due to the tethering effect of the ligament of Treitz, leaving this portion of the duodenum exposed to the direct pulsatile pressure of the aorta. Primary AEF has also been described in the following locations: esophagus (28%), small and large bowel (15%), and stomach (2%).⁷

Overall, the pathogenesis of primary AEF is uncertain. The proposed mechanisms are mechanical, infectious, and inflammatory (Fig. 51.1). In the majority of cases, the mechanical component is caused by the pulsatile pressure of an expanding aorta against the wall of the GI tract. This leads to local compression and ischemia, with weakening of the wall and eventual erosion with fistula formation.

SECONDARY AORTOENTERIC FISTULA

Incidence, Etiology, and Pathogenesis

Secondary AEF is more common than primary AEF and is related to prior open vascular surgery and endovascular repair, with an incidence of 0.36%⁸ to 1.6%⁹ reported after open abdominal aortic graft reconstruction. The interval from aortic reconstruction to onset of symptoms is on average 2 to 6 years after graft placement. Secondary AEF involves fistulization between the GI tract and a prior vascular reconstruction for either aneurysmal or occlusive disease. Although it is typically described as occurring in the setting of a synthetic graft, secondary AEF has also been reported with aortic homograft reconstruction and allografts. Similar to primary AEF, the most common location described for secondary AEF is the distal duodenum and proximal jejunum. However, secondary AEF has been described at multiple GI sites depending on the location of the prosthetic graft.

Secondary AEF has been further classified based on the location of the fistula regarding the suture line of the graft

(Fig. 51.2). A fistula that has a direct communication between the arterial circulation and the GI tract at the level of the suture line is classified as a graft enteric fistula. Communication between the GI tract and the graft interstices (but not at the suture line) is referred to as a graft enteric erosion. Both entities are highly morbid complications that require urgent management; however, the etiology and presentation may differ. The graft enteric fistula's involvement of the suture line will disrupt the arterial anastomosis and causes dramatic hemorrhage, whereas graft enteric erosion may be manifested first with infectious

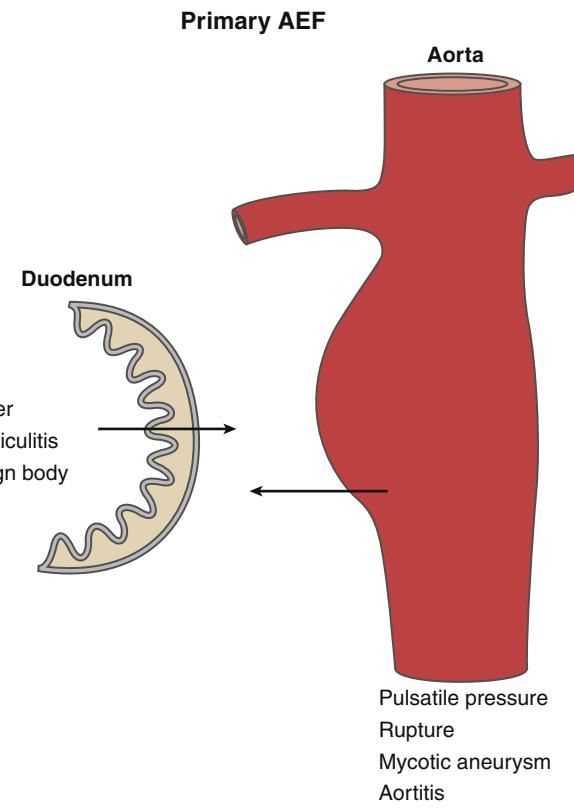


Figure 51.1 Etiologic Factors for Primary Aortoenteric Fistula (AEF). Pulsatile pressure from an expanding aneurysm is thought to be the predominant feature in the development of primary AEF. Other factors related to intrinsic bowel conditions may play a role in the development of primary AEF in a minority of cases.

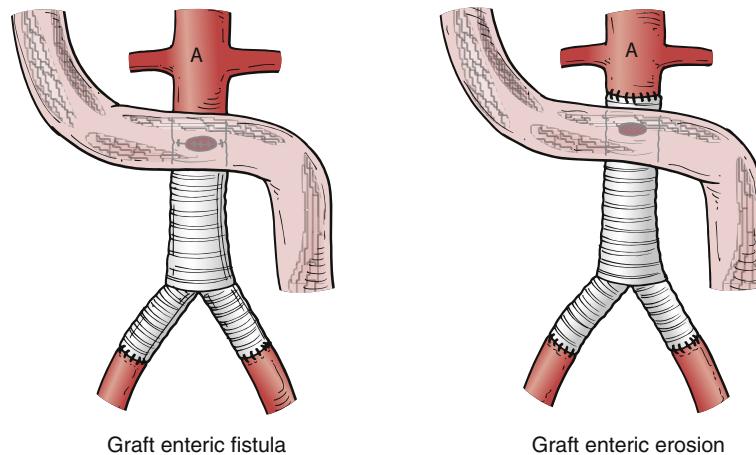


Figure 51.2 Graft Enteric Fistula Versus Graft Enteric Erosion. Graft enteric fistula has a communication between the bowel and the arterial circulation at the level of an arterial prosthetic suture line. Graft enteric erosion has a communication between the bowel and the interstices of an arterial prosthetic graft without involvement of the suture line.¹⁰

symptoms as a result of direct contact of the graft material with the GI tract, allowing bacterial translocation to occur between the interstices of the graft from the GI tract.

The etiology of secondary AEF includes both patient and surgical factors that occur during the initial placement of the graft. A history of multiple vascular procedures, wound complications, infection, emergency operation, and technical error have been found to predispose to secondary AEF formation.¹⁰

Pathogenesis

The proposed mechanisms of secondary AEF pathogenesis are infection, pulsatile pressure, and technical error.

Infection

Infection and downstream inflammation appear to play a significant role in the development of AEF. Studies lack uniformity in description of methods particularly in regard to bacterial culture which may differ between blood stream, graft, and aortic wall within these patients. Infection may result at the time of initial surgery, or through secondary infection and bacteremia. Further, varying immune and inflammatory features of patients may contribute to the development of graft infection and subsequent AEF. Best evidence suggests that secondary AEFs after open aortic reconstructions are polymicrobial in nature in upwards of two-thirds of patients.¹¹ Importantly, improved culture methods have demonstrated that yeast, particularly *Candida*, appear frequently in the setting of secondary AEF. *Candida* is also present in two-thirds of patients, with similar rates in patients who have undergone endovascular as compared to open intervention.^{11,12} Graft infection leads to local inflammation and results in breakdown of the suture line, pseudoaneurysm (PSA) formation, and eventual rupture into surrounding structures. It is important to acknowledge that characteristics of bacterial species, such as ability to produce collagenase and other locally destructive proteases, may contribute to the development of fistula complications. More research is required with improved bacterial methods to confirm this statement.

Pulsatile Pressure

Pulsatile pressure also remains a factor in the proposed mechanism of AEF formation. As described above, pressure from a noncompliant prosthesis against the bowel wall may lead to ischemia to the surrounding tissue and eventual erosion. Another mechanism described is suture line disruption, leading to the formation of an expanding PSA, compressing surrounding structures and eventually eroding into the bowel. Despite the intuitive nature of this mechanism, the majority of studies continue to point to the issue of infection as the root cause of AEF.

Technical Error

The final factor in the formation of AEF is technical error. This includes inoculation of the prosthesis at time of implantation as well as duodenal injury, serosal thinning, and ischemia during the operation. Changes in standards in patient preparation and appropriate antibiotic administration intraoperatively

have decreased the overall rate of aortic graft infection. Operative trauma to the bowel, however, remains an issue. The bowel can be injured during the initial dissection and exposure either directly with sharp injury and heat transfer from cautery or indirectly by over-retraction and tension. Retraction injury may occur from the retractor blades directly; however, it may also occur by over-compression of the bowel, causing ischemia, or by allowing the bowel to become dehydrated outside of the body. Methods to reduce bowel trauma include wrapping the bowel in warm moist laparotomy sponges during the procedure (being mindful to re-soak the sponges intermittently), keeping the bowel intraperitoneal by packing it above the liver (which can be difficult in larger patients), and using an isolation bag to keep the bowel moist and protected (but still visible) while it is outside the abdomen. Another method to reduce bowel trauma is by using a retroperitoneal approach and interposing tissue between the aorta and the graft at the end. Proponents of the retroperitoneal approach believe that avoiding division of the parietal peritoneum to expose the aorta limits the devitalization of tissue and development of adhesions between the graft material and bowel. Regarding interposition of tissue between the aorta and graft, aortic sac closure followed by a second layer of retroperitoneal tissue and parietal peritoneum is the preferred approach. If that is unavailable, a flap of greater omentum or a layer of bovine pericardium patch material may be used. Omental coverage may be necessary more commonly in end-to-side graft anastomoses to the aorta, rather than in end-to-end anastomoses, and in thin patients.

AORTOENTERIC FISTULA AFTER ENDOVASCULAR REPAIR

There are an increasing number of reports documenting AEF after endovascular aneurysm repair (EVAR) and thoracic endovascular aneurysm repair (TEVAR). Proposed mechanisms in the case of endovascular repair include persistent endoleak with growth of the residual sac, multiple coiling efforts to repair an endoleak, erosion of the stent-graft through the aorta, endotension, and infection at the time of graft placement.^{13,14} The Multicenter Study on Aortoenteric Fistulization After Stent Grafting of the Abdominal Aorta (MAEFISTO) evaluated 3932 patients who underwent EVAR between 1997 and 2013 at eight Italian centers with EVAR programs. Of the patients who underwent EVAR at the participating centers, 22 presented with AEF on follow up, 15 of which underwent EVAR for atherosclerotic aneurysmal disease and 7 for post-surgical PSA. On subgroup analysis, they found that the incidence of AEF development of EVAR was 0.46% in patients undergoing EVAR for atherosclerotic aneurysmal disease and 3.9% when performed for PSA. Anastomotic PSA as indication for EVAR, and urgent/emergency EVAR were significantly associated with AEF development. There were no significant associations between choice of endograft and fistula formation. The increased risk of AEF after EVAR for PSA does suggest that a preexisting infectious process or even subclinical AEF formation may have already been present at the time of EVAR placement in

these cases. In urgent/emergency surgery, the presence of a hematoma compressing surrounding structures or the overall increase in local inflammation in emergency repair may contribute to the formation of AEF.¹⁵ Most recently, systemic review of known AEFs after EVAR revealed that approximately 37% were associated with an endoleak and/or persistent sac expansion. Interestingly analysis of these devices identified that 30% of AEFs after EVAR were associated with a defect in the aortic stent graft that includes fracture, erosion, and angulation.¹⁶ As our endovascular experience continues to grow, it appears technical success at the initial operation may be an important factor in the prevention of AEF formation.

CLINICAL PRESENTATION

The classic clinical triad for primary AEF as described by Sir Astley Cooper in 1829 consists of GI bleeding, abdominal pain, and a pulsatile mass. Recent reviews note the incidence to be 64% to 94% for GI bleeding, 32% to 48% for abdominal pain, and 17% to 25% for a pulsatile abdominal mass, with all three of these symptoms occurring concurrently in only 11% of cases.¹⁷ Other symptoms reported include back pain, fever, and sepsis. Laboratory findings have been reported in only half of the studies, and only two-thirds of patients demonstrated a hemoglobin level lower than normal (8 mmol/L). One-quarter of patients had leukocyte counts above the upper limit of normal (10×10^9).¹⁸

In the case of secondary AEF, hemorrhage remains an important feature of the presenting symptoms. In a recent retrospective review of 4137 patients who underwent aortic reconstruction between 2000 and 2008, 37 patients (0.08%) presented with secondary AEF. Of these patients, 73% presented with some form of hemorrhage, 41% with sepsis, 22% with abdominal or back pain, 14% with graft limb thrombosis, 11% with a groin fistula, 8% with a peripheral abscess, 5% with a femoral PSA, and 5% with peritonitis.¹⁹

In both primary and secondary AEF, a classic clinical feature is the “herald bleed.” This is a minor bleed that is self-limited because of vasospasm and thrombus formation. Herald bleeds may lead to hospital admission immediately; however, some patients experience multiple episodes of recurrent bleeding. Regardless of the initial presentation, an untreated herald bleed is commonly followed by an exsanguinating bleed within hours to months.

By far the most important step in initial evaluation is a high level of suspicion. Given the rarity of the problem, there is frequently a delay in diagnosis of AEF. This delay leads to inappropriate timing of treatment and likely worse outcomes. Any patient with a history of AAA or graft placement presenting with occult anemia, GI bleed, or symptoms consistent with sepsis, should have AEF included in their early differential work up.

DIAGNOSIS

The diagnostic approach to the evaluation of AEF is dependent on the patient's hemodynamic status on presentation.

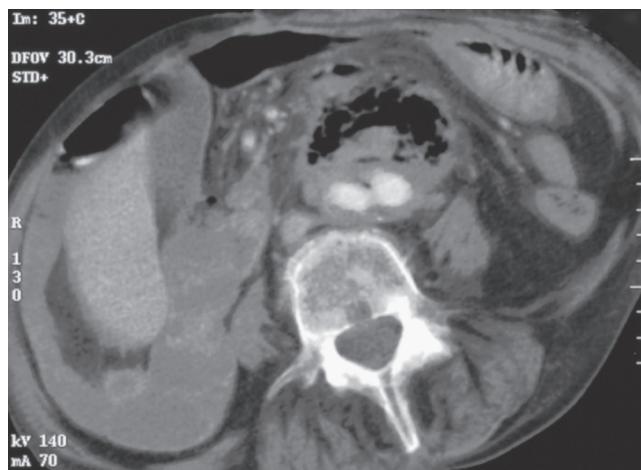


Figure 51.3 Contrast-enhanced computed tomography scan of a patient with a secondary aortoenteric fistula. Note the accumulation of gas and retroperitoneal inflammation surrounding a bifurcated aortic prosthesis.

In general, a high level of suspicion should be maintained in approaching any patient with massive GI bleeding and a history of an aortic aneurysm or previous aortic revascularization. In such cases of massive bleeding, diagnosis will often be made during exploratory laparotomy. If the patient is stable, the three major diagnostic modalities are computed tomography (CT) with iodinated contrast enhancement, esophagogastroduodenoscopy (EGD), and angiography. There has been some controversy in the past about which study should be done first; some authors have recommended EGD, followed by CT scan, followed by visceral angiography if no source is found. However, with the improvements of radiologic imaging, CT scan has become a preferred initial diagnostic test; CT scans are less invasive than EGD or angiography, are easy to obtain, and do not risk thrombus dislodgment.²⁰

Computed Tomography

Common findings on CT scan include effacement of the fat planes around the aorta, perigraft fluid and soft tissue thickening, ectopic gas (Fig. 51.3), tethering of adjacent thickened bowel loops toward the aortic graft, and, in rare cases, extravasation of contrast material from the aorta into the involved segment of bowel. Air within the aortic sac would also be highly suspicious after a postoperative period of at least 3 months.²¹ The detection rate of CT for AEF is the highest of all modalities (61%),¹³ and CT also can be used to assess the peripheral vasculature to assist with revascularization plans during repair. It is important to remember that use of oral contrast in these scans is not recommended as it will likely limit the ability to assess the endovascular repair (see Ch. 29, Computed Tomography).

Esophagogastroduodenoscopy

Endoscopy plays an essential role in the management of acute GI bleeding. Although it does not rule out AEF, it can exclude other sources of bleeding. The detection rate of AEF by EGD

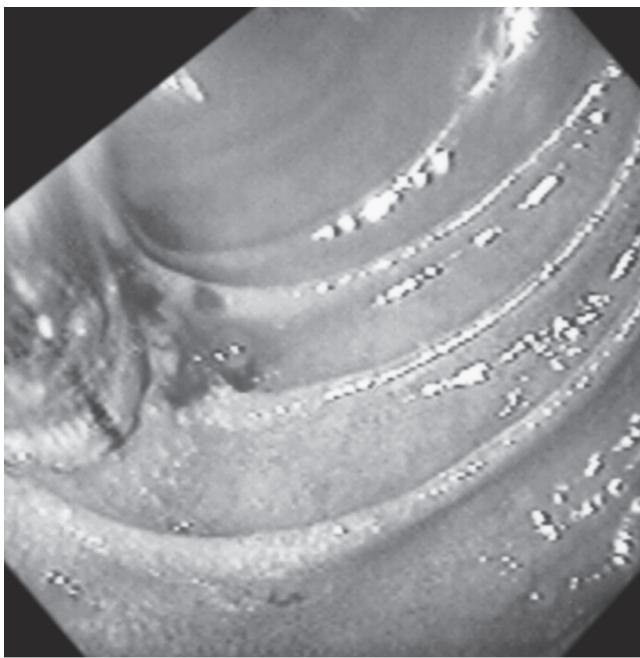


Figure 51.4 Esophagogastroduodenoscopy revealing an exposed Dacron graft that has eroded into the duodenum. Although this finding is unusual, esophagogastroduodenoscopy should be performed to visualize the fourth portion of the duodenum in most patients with gastrointestinal bleeding and previous aortic reconstruction.

is 25%, and it is essential that the third and fourth portions of the duodenum be visualized for a complete study. Endoscopy may be facilitated by using a pediatric enteroscope or a side-viewing endoscope, in addition to double balloon endoscopy for a more complete view of the GI tract. A careful study by an experienced endoscopist with a high level of suspicion may reveal a graft (Fig. 51.4), ulcer, erosion with adherent clot, or extrinsic pulsatile mass. This is uncommon, and as noted, the primary purpose of EGD is to exclude other pathologic processes as the source of GI blood loss. Only hemodynamically stable patients should undergo EGD, and some surgeons recommend that EGD be performed in the operating room so that laparotomy can be done should a tamponading thrombus become dislodged during the study and lead to severe hemorrhage.

Angiography

The role of angiography as a diagnostic modality for AEF is limited. It may be useful to delineate arterial anatomy for potential reconstruction and to identify secondary AEF by finding PSA formation at the proximal anastomosis of grafts (Fig. 51.5), kinking of graft limbs, or bulges in deteriorating prosthetic material. However, because a stable patient is likely to have an occlusive thrombus sealing the fistula at the time of the examination, its use in diagnosis is limited, with an AEF detection rate of 26%. As part of a treatment modality, angiography can be useful to place a proximal occlusion balloon prior to laparotomy.



Figure 51.5 Aortography revealing a secondary aortoenteric fistula arising from the proximal anastomosis of a bifurcated aortic prosthesis. Note the contrast material in the bowel lumen. Angiography is useful in planning reconstruction after graft excision but will only rarely document an aortoenteric fistula because most stable patients will have an occlusive thrombus sealing the fistula. (From O'Hara PJ. Surgical management of infected abdominal aortic grafts. In: Cowgill LD, ed. *Cardiac Surgery: State of the Art Reviews*. Philadelphia: Hanley & Belfus; 1987.)

Other Tests

Other tests, including leukocyte- and erythrocyte-tagged nuclear scanning, magnetic resonance imaging (MRI), ultrasound, and contrast-enhanced GI studies, are potentially useful but usually less accurate and more time intensive. Both MRI and magnetic resonance angiography may aid in the diagnosis of graft infection and AEF²² but are more difficult to perform in critically ill patients (see Ch. 30, Magnetic Resonance Imaging and Arteriography). Nuclear imaging techniques using indium In 111-labeled leukocytes²³ or immunoglobulin G²⁴ and technetium Tc-99m hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO)-labeled leukocytes²⁵ have high sensitivity in detecting graft infection, but their role in detecting AEF is less clear. Contrast-enhanced GI studies should be avoided, because they rarely help make the diagnosis, are time intensive, and can obscure findings in subsequent angiographic or contrast-enhanced CT studies.

A rare type of AEF is an aortoappendiceal fistula, which, given the location of the fistula and the quick transit time of blood through the large bowel, can cause patients to have bright red blood per rectum. In this situation, colonoscopy and tagged red blood cell scans may be needed for the diagnosis to be made.²⁶ Rarely, plain skeletal radiography reveals changes consistent with systemic infection. Unilateral lower limb hypertrophic osteoarthropathy^{27,28} and multifocal osteomyelitis²⁹ have also been associated with AEF.

TREATMENT

Conservative nonoperative therapy for AEF is uniformly fatal,³⁰ and surgery is the only treatment option with the potential for success. The important factors to be considered to coordinate effective surgical management are the presence of active hemorrhage, the classification of the AEF (primary or secondary), the presence of sepsis, and the anatomic distribution of the patient's aneurysmal or occlusive disease.

The first priority in treatment is to preserve the patient's life; the second is limb preservation. Whereas hemodynamically unstable patients with active GI hemorrhage or sepsis require urgent operative intervention, stable patients with a resolved herald bleed may be further evaluated and optimized. These patients must be monitored closely, however, and should proceed to surgery as soon as possible as the risk of fatal rebleeding is high; 30% of patients rebleed within 6 hours, and 50% of patients rebleed within 24 hours.¹³

Urgent Surgical Control of Hemorrhage

In instances of massive GI bleeding, central venous access, volume resuscitation, and broad-spectrum Gram-negative, Gram-positive, anaerobic antibiotic therapy in addition to anti-fungal coverage should be initiated. Anesthesia should be prepared for massive transfusion protocols, and aware of the complications of massive transfusion in these patients who often have severe comorbidities including congestive heart failure and lung disease. Further, close attention should be paid to the patient's temperature as hypothermia in the setting of stress, massive transfusion, and systemic heparinization can lead to fatal coagulopathy. The initial approach may be either open with a midline incision or endovascular control. If the surgeon is experienced, endovascular control may be initially preferred as it can be obtained while the patient is awake, limiting the side effects for anesthetic induction. Additionally, one should consider a brachial approach if significant scarring is present in the groins from previous intervention. Proximal control may be infrarenal or suprarectal, with supraceliac being favored in open operations. Distal control may be obtained with iliac clamping or occlusion balloons. Separation of the gastrointestinal fistula should be performed sharply and carefully as described in detail later. Once source control is obtained of the gastrointestinal tract, the focus should be directed to removal of the graft. Fixation elements of aortic endografts may make this difficult, and the author recommends moving the endograft proximally to allow release of the fixation elements, and gentle removal of the proximal portion of the endograft. Distal graft limbs are often more freely mobile as they lack fixation elements. In cases in which there is no evidence of local infection, *in situ* repair may be performed with a prosthetic graft, cadaveric artery, or femoral vein. If there is evidence of local infection, the aortic stump should be oversewn and covered with omentum. This should be followed by retroperitoneal debridement, drain placement, and extra-anatomic bypass.

Management of the Gastrointestinal Defect

As our understanding of management of AEFs has grown, it is apparent that management of the gastrointestinal defect is critical for a successful outcome. Postoperative GI complications with AEF repair have been found to independently increase mortality 3-fold.¹¹ Once the aorta has been controlled, the bowel should be sharply dissected off of the aneurysm/prosthesis. A portion of the graft may be left intact around the bowel in an effort to minimize contamination of the field. Alternatively, temporary repair of the defect can be attempted.

A review of aortoduodenal AEF bowel repair found higher rates of recurrent fistula formation after simple closure compared to complex (resection or diversion) bowel repair (48.9% vs. 11.1%, $P = 0.036$). On multivariate analysis, omentum (or any other structure) interposition between the bowel repair and artery was associated with lower mortality regardless of the technique used to close the bowel wall (OR 0.385, 95% CI 0.221–0.669).³¹ A recent study reported significant improvement in outcomes of management of AEF after identifying the detrimental effects of GI complications. Two general surgeons were utilized to perform enteric repairs. The focus was placed on re-approximation of the bowel with well-vascularized, tension-free edges after aggressive and wide debridement of tissue. Ultimately, more complex resections and anastomoses were performed rather than simple repairs. Additionally, the team paid close attention to early return to the OR for any concern for mesenteric ischemia. Impressively, 60-day mortality dropped from 53% to 8%.¹¹ Of note, no data exists comparing simple repair to resection and anastomosis for AEF.

Surgical Treatment in Stable Patients

In the case of a hemodynamically stable patient with no active bleeding, more time can be spent evaluating and planning the procedure. This allows the order of the operation to be reversed, with extra-anatomic bypass performed first (although initially a concern, the issue of graft infection of the newly placed prosthesis in the presence of a known infected abdominal graft has not been realized).^{14,32} This may be particularly useful in patients with known infection with a functional graft or in patients with anticipated prolonged clamp time, as it allows both limbs and the pelvic vasculature to remain perfused throughout the case, thereby reducing the risk of amputation and bowel ischemia. Cystoscopy with placement of ureteral stents can also be performed before laparotomy, which may assist in reducing ureteral injury during dissection in an inflamed retroperitoneum.

Primary Aortoenteric Fistula

Management of primary AEF depends on whether infection is present in the aortic bed at the time of surgical intervention. In the case of mild contamination, *in situ* replacement of the aorta with local debridement and long-term antibiotic and anti-fungal therapy is the favored approach. In the case of gross retroperitoneal contamination and sepsis, aneurysm

resection, omentoplasty, retroperitoneal debridement, and extra-anatomic bypass should be performed. The latter approach is considered inferior because of higher reported rates of mortality and limb loss, and most authors agree that it should be reserved for cases of gross contamination (defined as widespread aortic or retroperitoneal gross purulence or inflammation).³³

The majority of primary AEFs are in the duodenum and proximal small bowel, which is associated with less bacterial contamination because of differing flora and bacterial loads compared with more distal locations such as the colon. Regardless, all primary AEFs should be treated with antibiotics and anti-fungal agents in the postoperative period. Broad-spectrum antibiotics should be used until culture results are available, and then antibiotic therapy should be tailored appropriately. In the case of a negative culture, antibiotic therapy can be discontinued after 1 week; positive cultures necessitate a 4- to 6-week course.^{34,35}

Secondary Aortoenteric Fistula

The available operative choices for secondary AEF are graft excision alone, *in situ* replacement, graft excision and reconstruction with autogenous vein (i.e., the neo-aortoiliac system procedure), extra-anatomic revascularization and graft excision, and endovascular repair with lifelong antibiotics.

It is generally agreed that all infected synthetic material must be resected if there is clear evidence of graft and retroperitoneal contamination, which is more likely with AEF involving the distal GI tract and fistulae that have been chronic. The infected arterial tissue should be debrided back to grossly healthy tissue and closed with monofilament permanent suture material, preferably in two layers. The defect in the GI tract should be repaired with conventional techniques appropriate for the location of the fistula and retroperitoneal drains placed to minimize the risk of persisting sepsis causing breakdown or PSA formation at the site of arterial closure. If it is feasible, a flap of omentum should be placed to separate the bowel from the aortic stump closure and to fill the dead space resulting from excision of the graft. Despite this additional procedure, there still remains concern for the integrity of the aortic closure when infection is present. The aortic closure is at risk of “blowout,” which would lead to massive hemorrhage and a life-threatening emergency requiring emergent laparotomy.

Graft Excision Without Replacement

If the graft has been placed for occlusive disease or has been chronically occluded, it is possible to resect the graft without reconstruction. This will be possible only if the patient has sufficient collateralization, and CT or angiography may be helpful in assessing the patient preoperatively. If the original graft was placed in an end-to-side configuration, endarterectomy and patch angioplasty of the aorta and distal vessels may allow uninterrupted perfusion. Patch material such as vein or bovine pericardium should be considered. This approach should not be considered in patients with patent grafts, patients with

grafts placed for aneurysmal disease, or patients with palpable distal pulses. The concern in these clinical scenarios is that removal of the graft will lead to profound ischemia and the risk of amputation. The patient needs to be critically assessed for a means of arterial reconstruction that will allow adequate perfusion but not lead to a high risk of recurrent infection.

Extra-Anatomic Revascularization

Prior to the development of *in situ* graft replacement, extra-anatomic revascularization was one of few options available for repair of AEF. Extra-anatomic revascularization can be performed with externally supported (ringed) polytetrafluoroethylene and may be performed after abdominal closure with a fresh set of clean instruments to restore flow to the extremities. Alternatively, if the patient is stable and not actively bleeding, a preliminary extra-anatomic revascularization may be performed before the aortic procedure. This allows uninterrupted flow to the extremities throughout the procedure and reduces the risk of limb ischemia and amputation. The interval between the procedures should not be too lengthy, however, as there is the potential for graft occlusion due to competitive flow as well as recurrent GI bleed.

Regarding graft configuration, if the previous aortic synthetic graft reconstruction was intra-abdominal, axillofemoral grafting is feasible (Fig. 51.6). However, if the graft infection has extended to the femoral arteries, as in the case of previous aortobifemoral graft placement, bilateral axillo-unifemoral/popliteal grafts tunneled laterally to the available superficial femoral, profunda femoris, or popliteal arteries may be required. Tunneling of the left extra-anatomic bypass may be a problem if a left retroperitoneal incision was used for the initial graft excision. A variation on this approach involves the use of a composite graft consisting of placement of a synthetic

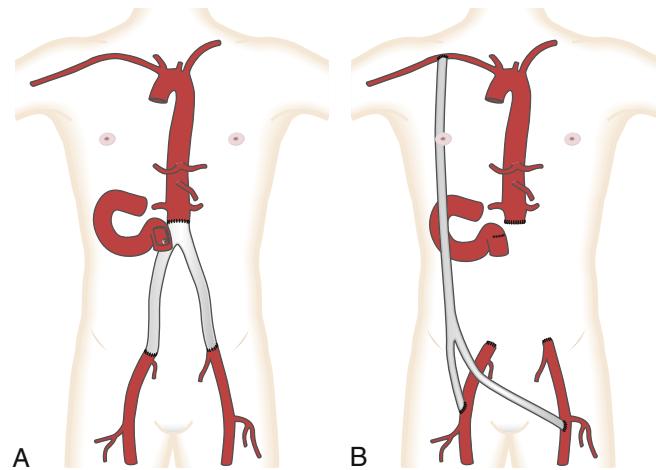


Figure 51.6 (A) Secondary development of aortoenteric fistula after synthetic aortobi-iliac graft placement. (B) Surgical management includes extra-anatomic bypass with an axillofemoral graft, resection of all abdominal prosthetic material, retroperitoneal debridement, and closure of the bowel defect. (Modified from O'Hara PJ. Surgical management of infected abdominal aortic grafts. In: Cowgill LD, ed. *Cardiac Surgery: State of the Art Reviews*. Philadelphia: Hanley & Belfus; 1987.)

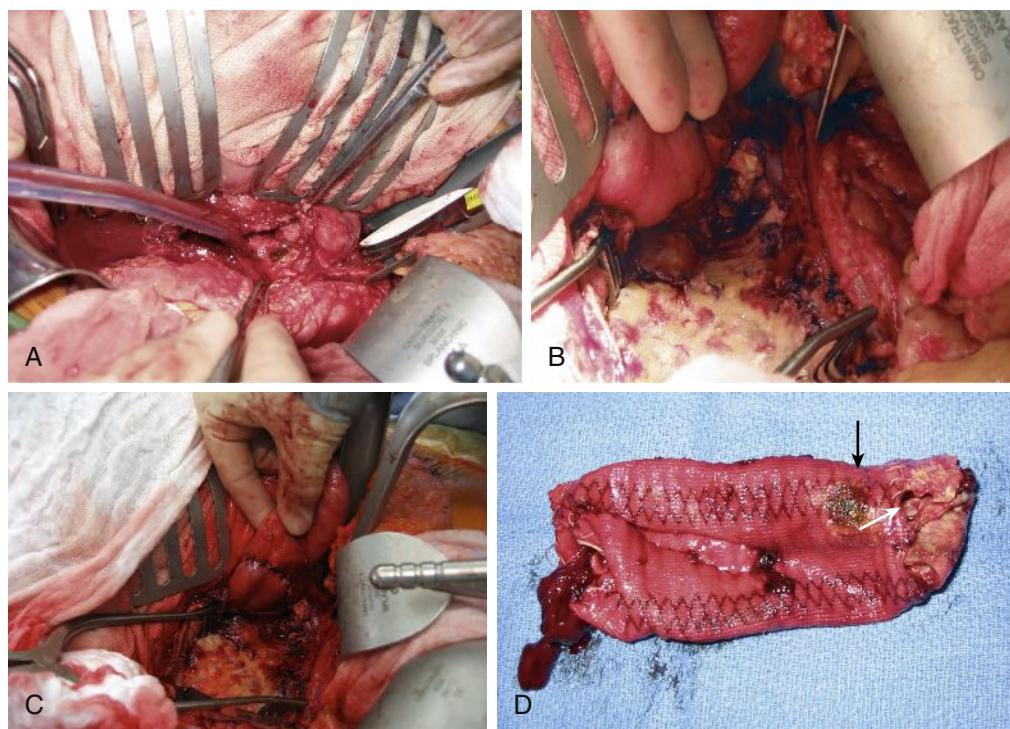


Figure 51.7 Intraoperative images of aortoenteric fistula repair with excision of aortic graft and extra-anatomic revascularization: (A) aortoenteric fistula *in situ*; (B) remaining aortic stump; (C) duodenal closure; (D) remnant graft with fistula site (arrow) next to the former proximal anastomosis. (Courtesy Robert Steppacher, MD.)

extra-anatomic graft in a noncontaminated tissue plane with the autogenous graft component extending to the debrided, contaminated femoral vessels. Care must be taken to avoid contamination of the synthetic component, and the surgeon should be familiar with techniques such as sartorius or rotational muscle flap rotation to provide adequate soft tissue coverage of the femoral vessels. Appropriate antibiotic coverage is important to minimize the risk of seeding the extra-anatomic bypass graft, which can occur in approximately 15% to 25% of patients.¹⁴ Long-term results of axillobifemoral bypass for AEF demonstrate findings consistent with poor patency, high amputation rates, and reinfection. Mortality rates range between 18% and 43% but are noted to be lower with staged procedures. Additionally, aortic stump rupture remains a concern and can be seen in up to a third of patients at the 3-month mark. Patency rates at the 5-year mark range from 64% to 80%.^{36–38}

In Situ Aortic Graft Replacement

In situ reconstruction may be attempted with use of cryopreserved allografts (Fig. 51.7), antibiotic-soaked synthetic graft, or silver-coated Dacron (see Ch. 49, Graft Infection). While once controversial, this technique has gained popularity in practice. Only one study currently exists comparing traditional axillobifemoral bypass to *in situ* reconstruction, and no superiority was found for either approach.¹⁹ Studies have also begun to demonstrate the potential benefit of *in situ* reconstruction; a meta-analysis in 2006 demonstrated a lower operative mortality for *in situ* reconstruction with rifampin-bonded prosthesis

compared with extra-anatomic reconstruction in patients with aortic graft infections.³⁹ Additionally, both antibiotic-soaked and silver-impregnated grafts have anti-microbial properties. A multicenter trial has demonstrated that cryopreserved allografts also demonstrate a low reinfection rate of approximately 14%.⁴⁰ Advocates of *in situ* reconstruction cite the following benefits: improved long-term patency, decreased risk of stump blowout, decreased risk of thrombosis ascending to the renal arteries after resection, and maintenance of blood supply to the colon and pelvis.

Neo-Aortoiliac System Procedure

The neo-aortoiliac system procedure uses the femoropopliteal vein to reconstruct an autogenous neo-aortoiliac system. Chung et al.⁴¹ have advocated this technique in the setting of graft infection, as it allows infection-resistant autologous tissue to be placed in the operative field and avoids the pitfalls of the aortic stump. Another benefit to this procedure is that use of autologous vein is relatively inexpensive compared with the use of cadaveric graft or other treated prosthetics, and it does not require lifelong anticoagulation as is the case with cadaveric allograft. The principal disadvantages of this procedure are the length of time required to harvest the deep vein and that it cannot be staged. Other drawbacks include the risk of venous insufficiency in the harvest limb leading to compartment syndrome and fasciotomy. These issues may be improved with multiple surgical teams and growing center experience. The two largest experiences to date using femoral veins for aortic graft infection management demonstrate varying results. In

one series, there was a higher rate of in-hospital complications and 50% mortality at 60 days, whereas in another report there was a decreased rate of AEF-related mortality using femoral vein as compared to other *in situ* reconstructions.^{11,12} The conflicting data further suggests the need for direct trials comparing various aortic reconstructions. The feasibility and utility of femoral vein graft in true AEF repair as compared to aortic graft infection remains to be determined.

Endovascular Repair

With the technical difficulty and resulting morbidity and mortality of current open operative approaches, endovascular repair offers an appealing solution, as it allows rapid control of hemorrhage with minimal physiologic impact on the patient. In the last decade, a growing number of case reports have described endoluminal stent-grafting (EVAR) for AEF. The use of endografting violates the basic principles of surgical treatment of AEF; the enteric fistula is not treated, the retroperitoneal tissue is not debrided, and the infected aorta/prosthetic graft is not removed. Despite this, a 2009 systematic review of the literature⁴² identified 33 reports that included 41 patients with AEF who had EVAR as initial management. In this review, all patients underwent successful endograft implantation, and 20% had concurrent repair (open or endoscopic) of the contributing portion of the GI tract. Not surprisingly, a significantly high complication rate was found after follow-up of 13 months, with 44% of patients developing persistent, recurrent, or new infection or hemorrhage and 29% of patients expiring, mainly as a result of septic complications. In the study, the major significant factors for poor outcomes were preoperative infection and complications that developed at any time after endovascular treatment. The overall conclusion of this study is that endovascular repair should be considered only a temporizing strategy until definitive repair can be performed. A similar conclusion was drawn from a multicenter retrospective study in 2011,⁴³ which reported the outcome of endovascular repair and open repair of AEF in 25 patients. The study found a statistically significant difference in overall morbidity in the short term (77% for open vs. 25% for endovascular); however, the early benefit of endovascular repair in the early operative period was lost by the second postprocedural year because of an increased recurrence of bleeding, sepsis, and AEF in the endovascular group. Despite these discouraging results, enthusiasm for endograft placement remains, and the practice of endograft placement with or without surgical management of the GI tract, long-term antibiotics, and “close surveillance” continues to be performed. This is particularly concerning, as recent reviews of the literature evaluating infectious complications after endograft placement have found that patients presenting with recurrent AEF or infection after endograft placement for the indication of AEF have uniformly fatal outcomes. In one study, which treated patients without explanation, but with antibiotics and surgical intervention for the bowel, 7/7 recurrent AEF patients died.³⁰ A second study, evaluating the outcomes of late open conversion for infected aortic endografts found that 6/6 recurrent AEF patients died.⁴⁴

In the case of aortoesophageal fistula, there has been interest in TEVAR as a means to control bleeding and reduce the 55.5% mortality associated with open repair of this condition. A 2014 meta-analysis documented similar overall mortalities for TEVAR alone; however, there was a significant decrease in mortality (52.5% vs. 25% [$P = 0.029$]) on univariate analysis when the TEVAR was used as part of a combined approach (e.g., with a staged graft excision and esophageal resection or staged esophageal resection and debridement). This report also noted a decrease in mortality, bleeding, and AEF recurrence with the use of greater than 4 weeks of antibiotic on multivariate analysis (OR 0.03, 95% CI 0.001–0.21, $P = 0.0039$).⁴⁵

In summary, endovascular repair should be reserved as a bridge to open repair once patients have stabilized and local infection control is established. It is also an acceptable treatment modality for patients with a limited life expectancy who would benefit from a short hospital stay and earlier discharge and will not be exposed to the long-term risks.⁴⁶

RESULTS AND CONCLUSIONS

In primary AEF, standard aortic reconstruction with repair of the associated bowel defect has been successful in many cases. In a collective review of 118 cases, nonoperative management was uniformly fatal.³⁵ Thirty-three patients were treated surgically, with an operative mortality of 36%. Standard aortic reconstruction with duodenal repair was performed in 19 of 22 survivors with minimal long-term sequelae.³⁵ Similar results have been reported in an additional 35 cases in the Netherlands, thus indicating that placing a prosthesis in patients with primary AEF appears to be safe.⁴⁷

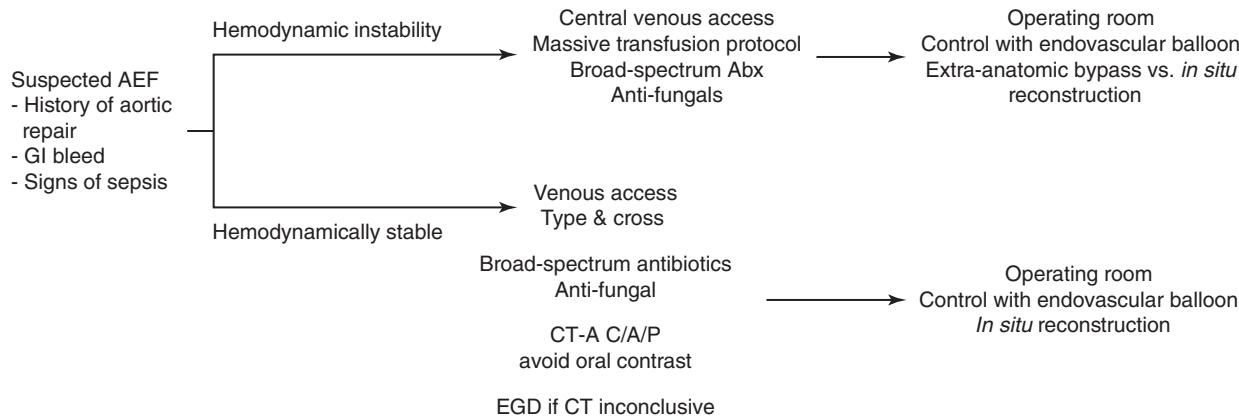
The natural history of untreated secondary AEF is hemorrhage, continued sepsis, and eventually death. Operative mortality ranges from 13% to 86%, with an average mortality of 30% to 40%. Amputation rates are approximately 10%, and long-term survival approximates 50% at 3 years. Taken together, these results attest to the tremendous physiologic stress from the AEF itself and the magnitude of operative repair of AEF. Of note, multiple authors have documented higher mortality rates in patients treated for AEF than in those treated for aortic graft infection alone. In a report of 61 patients, AEF operative treatment required longer hospitalization and more blood transfusion. Furthermore, operative mortality was higher (35% vs. 17%), and 12-month survival diminished (25% vs. 60%) for AEF versus aortic graft infection.⁴⁶ While large databases exist for surgical experience of aortic graft infections, it remains unclear as to whether or not these data are useful in the setting of AEF pathology.

Multiple strategies have been advocated for the operative management of AEF, and controversies continue to abound. In the appropriate patient with chronic graft occlusion or severe aortic occlusive disease, simple graft excision may be the only treatment required. *In situ* repair with allograft, antibiotic-impregnated graft, or silver-coated graft has become increasingly performed in the appropriate patient population, as has the neo-aortoiliac system procedure. Extra-anatomic reconstruction remains a safe alternative in the setting of gross

contamination and can be particularly useful if it can be staged before the aortic graft resection. EVAR continues to be performed and has the greatest potential to minimize overall morbidity and mortality; however, it currently remains a temporary

measure to bridge patients to definitive repair. In summary, the key features to successful treatment are timely intervention, appropriate patient selection, effective bowel repair, and long-term follow-up.

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Local Endovascular Complications and their Management

JEFFREY J. SIRACUSE and JAMES F. MCKINSEY

INTRODUCTION	664
ACCESS SITE COMPLICATIONS	664
Groin Hematoma	664
<i>Etiology and Manifestations</i>	664
<i>Management</i>	664
Retroperitoneal Hematoma	665
<i>Manifestations and Diagnosis</i>	665
<i>Management</i>	665
Arteriovenous Fistula	665
<i>Etiology, Manifestations, and Incidence</i>	665
<i>Management</i>	666
Pseudoaneurysm	666
<i>Etiology and Manifestations</i>	666
<i>Management</i>	667
ULTRASOUND-GUIDED THROMBIN INJECTION	667
SURGICAL MANAGEMENT	667
Thrombosis	667
UPPER EXTREMITY ACCESS COMPLICATIONS	667
Axillary and Brachial Artery Injuries	667
Nerve Injury	667
Thrombosis	668
Radial Artery Access Complications	668
Pedal Access	668
PERCUTANEOUS CLOSURE DEVICE COMPLICATIONS	668
Perclose	668
StarClose	669
Exoseal	669
Angio-Seal	669
Mynxgrip (Mynx)	669
BLEEDING COMPLICATIONS	670
ISCHEMIC COMPLICATIONS	670
PROCEDURE-SPECIFIC COMPLICATIONS	670
Dissection	670
<i>Balloon Angioplasty Dissection</i>	670
<i>Subintimal Angioplasty</i>	671
Embolization	671
<i>Management</i>	671
Perforation	672
<i>Wire Perforation</i>	672
<i>Angioplasty Perforation</i>	672
<i>Atherectomy Perforation</i>	673
Endovascular Aneurysm Repair Access Site	673
OTHER ENDOVASCULAR PROCEDURE COMPLICATIONS	674
Thrombolytic Therapy Complications	674
Device Infection	674
<i>Stents and Endovascular Stent Grafts</i>	674
Device Fracture or Embolization	674
Venuous Procedures	674
<i>Angioplasty and Stenting</i>	674
<i>Inferior Vena Cava Filter Complications</i>	675
COVID-19 Considerations	675
CHAPTER ALGORITHM	XXX

INTRODUCTION

Endovascular procedures are often the first intervention for peripheral arterial disease and many other vascular surgical conditions.^{1,2} Although these are thought to be less invasive and “safer,” endovascular interventions can have unique complications that surgeons and other interventionalists should be aware of and be prepared to expeditiously treat.^{3,4} These complications can range from minor ones, that can be treated with minimally invasive intervention, to serious life or limb-threatening conditions that require emergency operative or percutaneous interventions. Although the majority of percutaneous arterial peripheral interventions have been performed with common femoral artery access, alternative sites such as radial and pedal access are becoming more common.^{5,6} Access site complications are the most common complications, with rates up to 6% having been reported.^{1,7,8} Other complications can involve target vessels as well as downstream targets. Predicting which patients are at greatest risk for access site injury is crucial for the interventionalist. Risk factors for access site complications are listed in Table 52.1.^{9–11} By identifying higher-risk patient groups, risk reduction strategies can be implemented and complications can be decreased.

ACCESS SITE COMPLICATIONS

Groin Hematoma

One of the most common complications of percutaneous access is the development of a groin hematoma.¹ The clinical manifestations of a groin hematoma vary widely. In most circumstances, post-procedure groin swelling or ecchymosis are the only clinical findings. Other common signs and symptoms include pain, bleeding at the puncture site, neuropathy secondary to nerve compression, anemia and, in more advanced cases, hypotension.

Etiology and Manifestations

Hematomas can result from difficult access, multiple access attempts, or inadequate closure or compression at the completion of the procedure.^{12,13} For access, adequate compression should be used after an attempt to obtain hemostasis and this can be variable based on needle size. Further, back wall injury or leakage around the sheath can contribute to hematoma formation. Routine ultrasound use has been shown to decrease the risk of post-procedure hematoma. Routine and selective ultrasound guidance was used by 27% and 73% of interventionalists in the Vascular Study Group of New England.¹² The overall post-procedural groin hematoma rate after PVI was 4.5%. However, the rate of combined moderate and major hematoma was 0.8%. Ultrasound-guided access was protective against hematoma overall and particularly in patients aged greater than 80 years, obese patients, and those with a sheath size >6F.^{12–14} Larger sheath size has been associated with minor, but not major hematoma, development.¹³

Management

Treatment strategies for groin hematomas generally consist of observation as well as correction of any underlying

TABLE 52.1 Risk Factors for Access Site Complications^{9–11}

Advanced age
Warfarin use
Congestive heart failure
Non-ultrasound guided access
Large sheath size
Intervention performed
Emergent case
Chronic obstructive pulmonary disease
Antiplatelet use
Hypertension
Tibial interventions

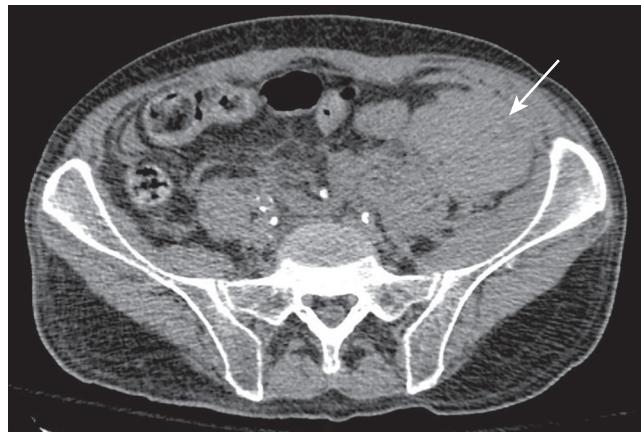


Figure 52.1 Left groin hematoma (arrow) after percutaneous access.

coagulopathy. Transfusion may be required. Manual compression should be applied to hematomas that have been identified in the acute setting. Similarly, mechanical compression devices such as the FemoStop (Radi Medical Systems, Wilmington, MA) or C-clamp have demonstrated benefit in reducing bleeding complications.¹⁵ Computed tomography (CT) can be useful to assess the extent of the hematoma, the level of the defect, and to assess for active bleeding as evidenced by a contrast-induced blush (Fig. 52.1). Moreover, imaging is prudent with large hematomas to rule out extension into the retroperitoneum, especially when associated with hemodynamic instability. In cases without hemodynamic instability or retroperitoneal bleeding, laboratory assessment of hematocrit levels should be performed every 4 to 6 hours until stabilization. Furthermore, interval duplex assessment should be performed to rule out the development of a pseudoaneurysm.^{15–18} Although most of these patients can avoid an intervention, time to ambulation is delayed and length of stay tends to be longer.^{15–18} The incidence of hematomas requiring transfusions in the coronary literature have been reported as 1.8% and was associated with both in-hospital mortality and 1-year mortality.¹⁸ Groin exploration with evacuation of the hematoma is warranted in the setting of hemodynamic instability, persistent anemia despite transfusions, skin necrosis, nerve compression, or severe pain.

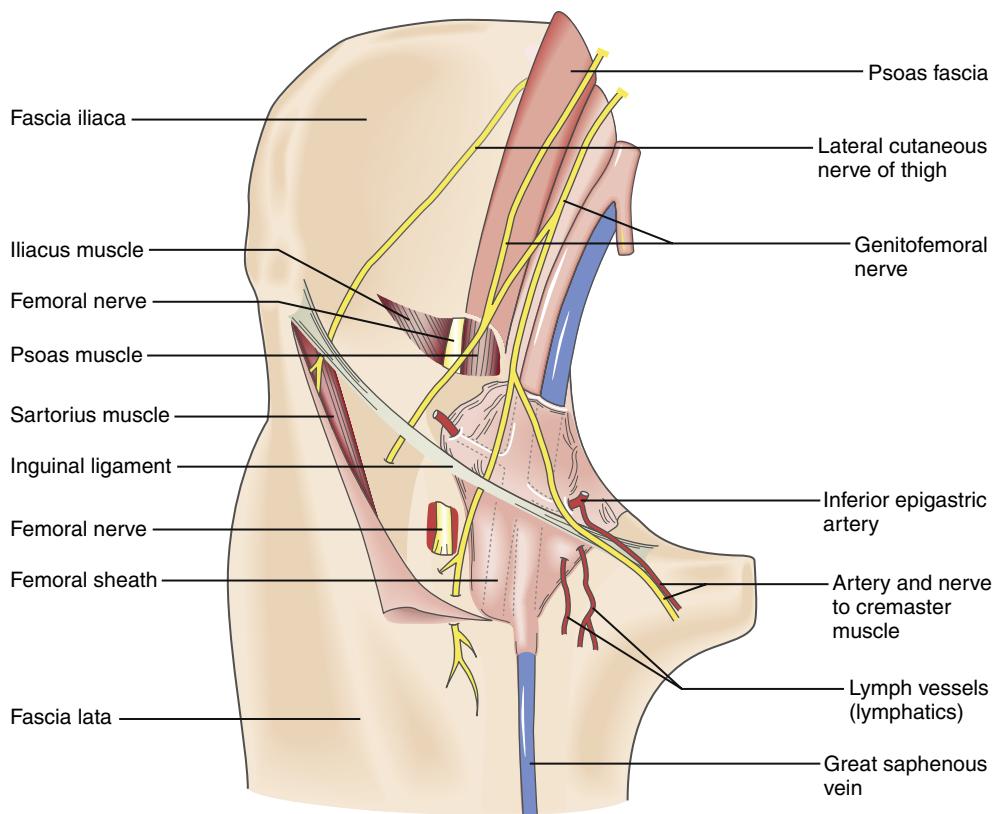


Figure 52.2 Relative anatomy of common femoral artery for access.

Retroperitoneal Hematoma

High punctures at the groin, particularly above the most inferior border of the inferior epigastric artery, present increased risk for the development of access site complications, including retroperitoneal hematoma.¹⁹ Though rare, a retroperitoneal hematoma has the potential for severe morbidity and even death if not detected. Retroperitoneal hemorrhage is associated with in-hospital cardiovascular events and mortality. Bleeding that extends into the retroperitoneum is less likely to be tamponaded by surrounding structures (Fig. 52.2). Independent factors associated with retroperitoneal hematoma include male sex, anticoagulation use, low body surface area, <1.73 m², and higher femoral artery puncture.^{17–20}

Manifestations and Diagnosis

Clinical findings of retroperitoneal hematomas are often subtle and less obvious than with groin hematomas. The most common symptoms are hypotension followed by diaphoresis, groin pain, abdominal pain, bradycardia, and back pain.¹⁷ The diagnostic test of choice for retroperitoneal hematoma is abdominopelvic CT (Fig. 52.3).

Management

Treatment for a retroperitoneal hematoma is tailored to the clinical status of the patient. Indications for intervention include neurologic deficits in the affected extremity, hemodynamic instability, ongoing blood loss, and severe pain.²¹ Decompression of a retroperitoneal hematoma can be performed

either through a groin incision or through an incision above the inguinal ligament to gain direct access to the retroperitoneum and iliac vessels. The arteriotomy must be exposed and repaired for optimal therapy. A covered stent can also be used to obtain control of bleeding especially if the arterial injury is above the inguinal ligament, avoiding a more morbid operation both for small and large bore femoral artery access.^{22–24} Care should be taken to avoid covering the deep femoral artery.

Arteriovenous Fistula

Etiology, Manifestations, and Incidence

An arteriovenous fistula (AVF) in the groin is a rare complication of percutaneous access and involves a communication between the femoral artery and vein. The incidence has been reported as 0.5%–0.86%.^{25,26} AVF after coronary interventions has been associated with high heparin dosage, warfarin use, left-sided access, hypertension, simultaneous femoral artery and vein access and female gender. Within 12 months, 38% of all AVF closed spontaneously. None of the risk factors for AVF influenced the incidence or the rate of AVF closure.²⁵ An AVF usually occurs after inadvertent low puncture of the CFA bifurcation or the profunda femoris artery and vein, which run near the superficial femoral artery (SFA). However, an AVF may also develop after through-and-through puncture of the CFA or SFA into the common femoral vein. Groin AVFs are generally asymptomatic and detected on physical examination by the presence of a palpable thrill in the groin or auscultation

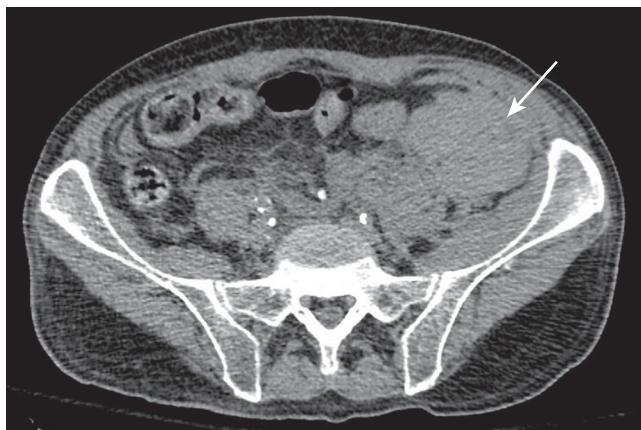


Figure 52.3 Left retroperitoneal hematoma (arrow) after left common femoral artery access.

of a continuous bruit. Duplex ultrasound is the imaging study of choice and demonstrates the characteristic systolic–diastolic flow pattern with arterialization of the venous signal (Fig. 52.4).

Management

Treatment options include observation alone, surgical repair, and endovascular repair. Ultrasound-guided compression had historically been used to treat groin AVF, but success rates have been low.²⁷ If conservative management is implemented, patients should have follow-up duplex surveillance and physical examination. Symptoms can include distal ischemia or cardiac dysfunction. If symptoms arise or the fistula increases in size, surgical treatment is indicated. Endovascular management of femoral AVFs has been reported with the advent of balloon-expandable stent grafts.^{28–31} Coverage of the fistula with a covered stent graft results in immediate abolition of the AVF without the need for surgery and therefore is optimal for high-risk candidates who may have failed conservative management. There have been published series using thrombin injection, although there can be a risk of arterial or venous embolization. The decision whether to treat an AVF with open, endovascular, or conservative measures is still under debate and should be driven by surgeon experience and the patient's overall symptomatology and comorbid conditions.

Pseudoaneurysm

Etiology and Manifestations

A pseudoaneurysm (PSA) may develop post-procedure if the arteriotomy has not adequately sealed once the sheath is removed. There is communication with the arterial lumen, and blood spreads into the surrounding soft tissue. It is a “pseudo” aneurysm in that no elements of the arterial wall are incorporated in the aneurysm sac; the wall of the PSA consists solely of compressed thrombus and surrounding soft tissue. PSAs can be differentiated from hematomas by arterial flow into the PSA with a defined neck that tracks to the arteriotomy.

The incidence of PSA formation after percutaneous procedures in contemporary series is less than 1%.^{9,32} The cause of a PSA is often related to an inability to adequately

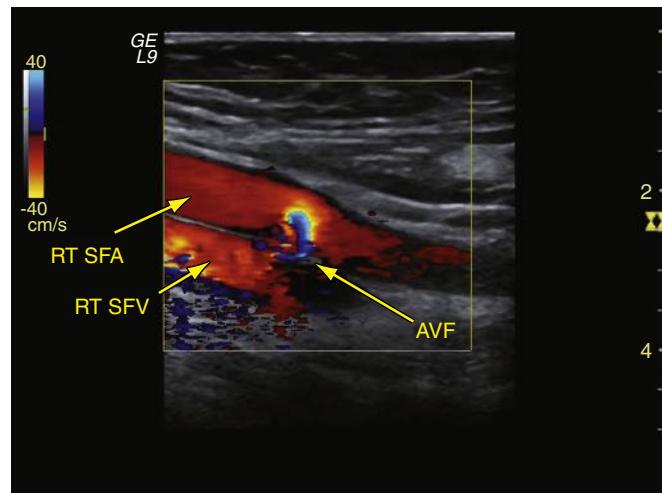


Figure 52.4 Duplex demonstrating the characteristic systolic–diastolic flow pattern seen with a femoral artery to vein arteriovenous fistula.

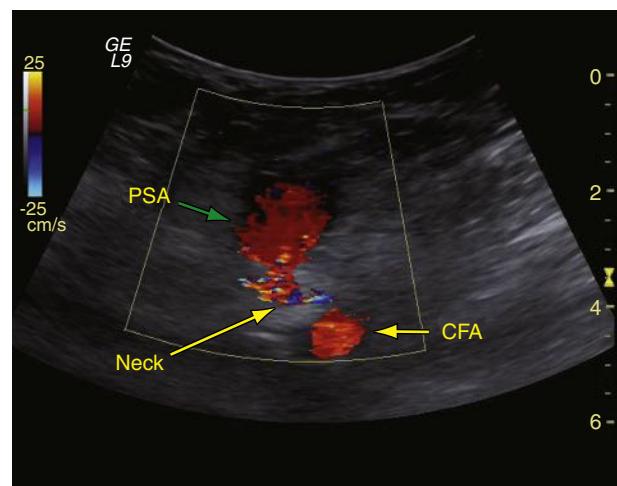


Figure 52.5 Duplex of a femoral artery pseudoaneurysm.

compress the vessel or closure device failure after removal of the sheath. This occurs most frequently with SFA or low CFA puncture because the femoral head sits more cephalic and compression is insufficient. Other associated risk factors include older age, female sex, obesity, larger sheath size, anti-coagulation and antiplatelet use, and manual compression.³³ On physical examination, a systolic bruit can be auscultated and is associated with the pulsatile groin mass. When there is clinical suspicion of a PSA, groin arterial duplex examination should be performed (see Ch. 22, Vascular Laboratory: Arterial Duplex Scanning). The typical ultrasound appearance of a PSA is an echolucent sac that is pulsatile, and with the addition of color Doppler, a swirling flow pattern is noted within this sac (Fig. 52.5). On spectral waveform analysis the characteristic “to-and-fro” flow pattern can be discerned and is pathognomonic for PSA.^{34,35} If the PSA has significant extension into the retroperitoneum, abdominopelvic contrast-enhanced CT may be of benefit to evaluate its size, as well as identify additional arterial injury sites (see Ch. 29, Computed Tomography).

Management

Historically, an open operation was the primary recommended therapy for large or expanding PSAs to decrease the complications of nerve compression, distal embolization, or skin necrosis. Contemporary treatment is often minimally invasive, and ultrasound guided compression has been advocated. In the largest series published to date, success rates ranged from 74% to 93%.^{36–38} The main factors impeding successful ultrasound-guided compression include anticoagulation at the time of compression, size of the PSA, and patient discomfort. Risks associated with ultrasound-guided compression include PSA rupture, distal embolization, and thrombosis of the femoral vein or artery.^{38,39}

Ultrasound-guided thrombin injection

The disadvantages of ultrasound-guided compression, including patient and ultrasound technician discomfort and only moderate success, prompted the development of a new therapy consisting of injection of thrombin directly into the PSA under ultrasound guidance. The principle of this technique is based on the necessity of thrombin for conversion of fibrinogen to fibrin. When blood is exposed to high-dose thrombin within the aneurysm sac, fibrin clot forms and instantaneously results in thrombosis of the PSA. It should be noted, however, that this still remains an off-label use for thrombin, which was produced as a topical hemostatic agent.^{39–42} Lönn et al. performed a randomized prospective study comparing thrombin injection to compression.⁴² Thrombosis within 24 hours was achieved in 15 (100%) patients given thrombin versus 2 (13%) in the compression group ($P < 0.001$). The most significant complications of this procedure include thrombosis of the native artery or vein if thrombin is inadvertently injected into these vessels. Anaphylaxis has also been reported anecdotally, especially with bovine preparations of thrombin, but this complication is very rare.⁴³ Failure of PSA closure by thrombin injection was associated with larger diameter of PSA and neck length and diameter greater than 0.55 cm. Anticoagulation use is also associated with incomplete thrombosis.^{44–46} For PSAs that are small, observation alone is a reasonable treatment strategy.^{47,48}

Surgical management

Despite the excellent results with thrombin injection, there still remains a role for surgical repair of PSAs. These include larger pseudoaneurysms and those without a narrow neck, and those that have failed compression or thrombin injection. Techniques of PSA repair include direct surgical repair and endovascular options.^{49,50} Endovascular options for post-angiography PSA exist, including using a covered stent for both small- and large-bore access have been described with good results.^{51–53}

Thrombosis

CFA thrombosis at the site of an endovascular procedure is a known complication of catheter-based interventions. Simple compression of the CFA after removal of the sheath can lead to thrombosis, especially in the presence of significant CFA atherosclerotic disease or previous groin reconstruction. CFA

occlusion in a contemporary series in the treatment of critical limb ischemia in the Vascular Quality Initiative was 0.2%.¹ Thrombosis usually becomes apparent after the sheath has been removed and manual compression has been completed. Treatment consists of groin exploration with femoral endarterectomy, patch angioplasty, and thromboembolotomy. Alternatively, patients may benefit from endovascular interventions, including mechanical thrombectomy, thrombolysis, or atherectomy, to remove or dissolve the obstruction.

UPPER EXTREMITY ACCESS COMPLICATIONS

Axillary and Brachial Artery Injuries

Although the vast majority of peripheral interventions are performed through the groin, severe atherosclerotic disease of the femoral or iliac vessels can often make this approach difficult. As an alternative, the brachial and axillary arteries have demonstrated adequacy as access vessels to perform lower extremity, visceral, or carotid interventions. These are becoming more frequent with complex aneurysm repair. In the Vascular Quality Initiative, brachial access was performed in 1.6% of procedures. Brachial access was associated with an increased complication rate compared with femoral access (9.0% vs. 3.3%; $P < 0.001$), including more hematomas (7.2% vs. 3.0%; $P < 0.001$) and access site stenosis/occlusion (2.1% vs. 0.4%; $P < 0.001$). Neither surgeon's overall peripheral vascular intervention experience nor prior experience with brachial access predicted likelihood of adverse events.⁵⁴ Larger sheath sizes (>5 F), percutaneous access, and female gender were risk factors for complications. In a cardiac catheterization study in which up to 7-F sheaths were used, the major complication rate was approximately 5%.⁵⁵ In evaluating the transaxillary approach, Chitwood and associates found a 2.3% incidence of complications, and the most common was nerve injury.⁵⁶ Large-bore percutaneous axillary artery access has been described with good results for complex endovascular aortic aneurysm repair.^{57,58} Axillary conduits can be safely used to facilitate access, however they do have a small risk of stroke and hematoma.⁵⁹

Nerve Injury

It is important to maintain high vigilance for nerve injury with transbrachial/transaxillary access because of the potential for permanent devastating disability of the upper extremity. When compared with the groin, where the incidence of nerve injury from percutaneous procedures is extremely low (0.2%), brachial access can be associated with clinically significant neuropathy of the various terminal nerves of the infraclavicular brachial plexus at an incidence ranging between 0.4% and 12.7%.^{60,61} This neuropathy probably occurs because anatomically the median nerve and brachial artery are in close association and travel within the medial brachial fascial compartment (Fig. 52.6). Patients complain of pain radiating down the arm with associated muscle weakness and paresthesias. The most common and treatable cause of neurologic dysfunction is compression from

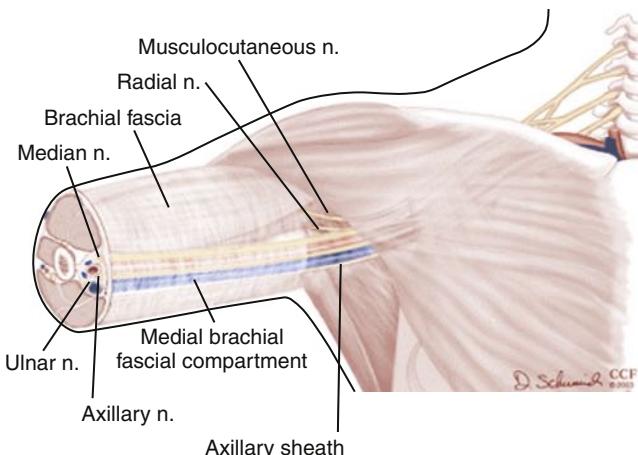


Figure 52.6 Relative anatomy of the brachial and axillary arteries.

an axillary sheath hematoma. Treatment involves decompression of the fascial compartment with exposure of the brachial artery and repair of the arteriotomy.

Thrombosis

The small diameter of the brachial artery makes it more prone to thrombosis. The diagnosis may become evident if the patient complains of hand symptoms, including pain, numbness, or tingling. This should prompt rapid removal of the sheath. For closure, manual compression should be applied with just enough pressure to prevent bleeding and hematoma while maintaining perfusion to the hand.

Radial Artery Access Complications

Radial artery access is becoming increasingly common for cardiac, neurovascular, and peripheral vascular interventions.^{62,63} Radial access has been shown to be safe and many specialties have adopted the technique, especially cardiology and neuroradiological radiology. Vascular surgeons have used this particularly for renal, visceral, and iliac interventions with limitations for more distal interventions. Pseudoaneurysm is one of the most common complications and may require open repair.⁶⁴ Radial artery occlusion is seen post-procedure at a rate of 7.7% at 24 hours, which decreased to 5.5% at >1 week follow-up. Higher doses of heparin, shorter compression time, advanced age, female gender, sheath size, and smaller diameter of radial artery have been shown to be associated with radial artery occlusion.⁶⁵ Radial artery occlusion is often without clinical sequelae due to collaterals in the hand.⁶⁶

Pedal Access

Retrograde pedal access is more often used for tibial lesions that cannot be crossed antegrade or retrograde. Treatment could be accomplished either by snaring from above and treating antegrade or by placing a sheath in the pedal vessels. Sheaths up to 6F have been successfully used as the sole access site to treat femoropopliteal lesions.⁶⁷ Several retrospective

analyses have demonstrated similar access site and target vessel peri-procedural complication rates to traditional access.^{68,69} However, it is unclear about whether the target vessel for revascularization is altered long-term.⁷⁰⁻⁷²

PERCUTANEOUS CLOSURE DEVICE COMPLICATIONS

Vascular closure devices (VCDs) allow for rapid arteriotomy closure after percutaneous interventions. They allow early ambulation and discharge after groin puncture and mitigate patient discomfort from extended manual compression. In addition, when compared with manual compression, which requires normalization of the activated clotting time (ACT) before pulling the sheath, VCDs are used immediately once the procedure has concluded. However, despite the obvious benefits of VCDs, they have not gained universal adoption among interventionalists. A Cochrane analysis of 52 studies showed that VCDs were associated with reduced time to hemostasis when compared with extrinsic compression. No deaths were reported secondary to VCDs. There were no differences in the incidence of infection between closure device type and extrinsic compression. Limited data were obtained when VCDs were compared with each other.⁷³ Traditionally, closure devices were used for the common femoral artery for retrograde access, however they are increasingly being used for antegrade access and for percutaneous axillary artery access.^{58,74}

Perclose

The primary suture-based closure device is the Perclose (Abbott Vascular, Redwood City, CA). It is a 6-F sheath-mediated VCD that fires a single monofilament polypropylene suture. For sheath sizes greater than 8F, more than one device is recommended. A prospective randomized study looking at the Perclose Proglide device compared to manual compression showed that there was shorter time to hemostasis, ambulation, and discharge with suture-mediated closure. There was no difference in overall complication rate between the two treatment groups.⁷⁵ Perclose is increasingly used to “preclose” the common femoral artery before endovascular aortic aneurysm repair (EVAR). Technical success rate of approximately 90% have been reported. Device failure can be treated with manual compression, additional Perclose use, or open repair. This technique has been associated with shorter operative time and postoperative length of stay.⁷⁶ After the completion of the large-bore access endovascular procedure, we have adopted a technique of setting down the Perclose sutures without locking the knots and then placing the outer dilator over the wire and performing a completion ipsilateral oblique angiogram. If there is an extravasation, closure-related stricture or dissection, it can be immediately addressed before the patient leaves the interventional suite. If there is a stricture the interventionalist can cut the unlocked suture and the remove one of the Perclose sutures to see if that will make an improvement in the arterial stricture. If after the removal of one suture there

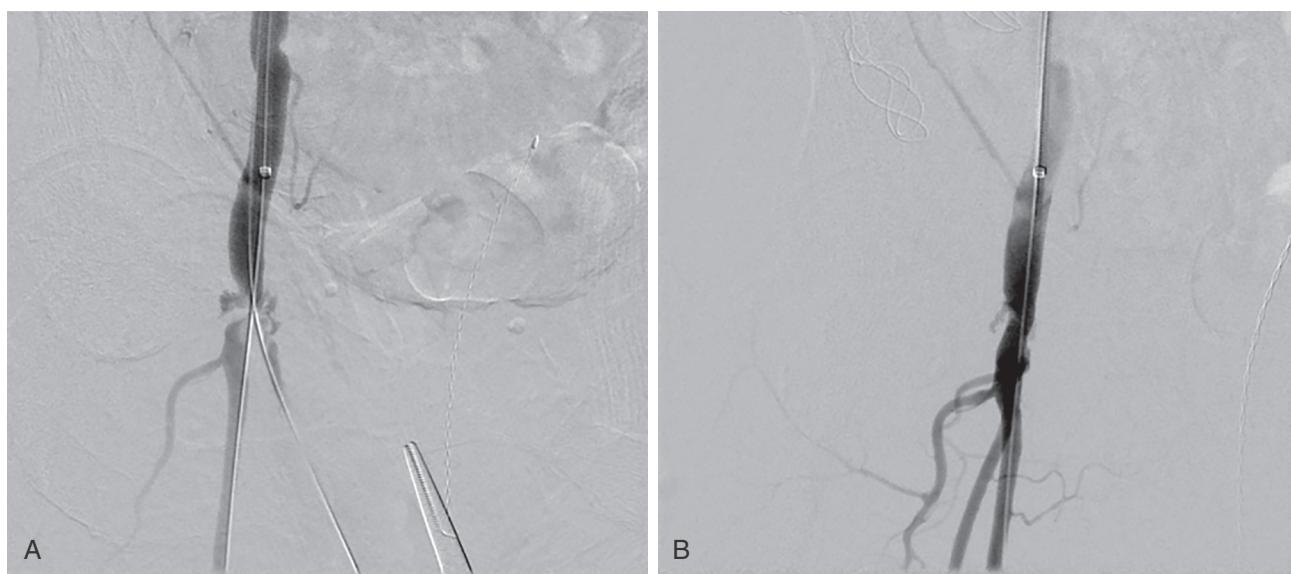


Figure 52.7 (A) Stricture after double pre-close for large bore (22 F) access, wire access maintained. (B) Resolution of stricture after subsequent angioplasty.

is extravasation from the closure site, pressure can be applied while an additional Perclose device is prepared and deployed. In rare cases, a contralateral angioplasty balloon can be positioned across the stricture and balloon dilation performed (Fig. 52.7). An additional Perclose device should be ready for deployment if necessary or conversion to open repair. If open repair is required, a sheath can be reinserted over the wire to allow for hemostasis while the cut down is carried out. It is critically important that wire access is maintained across the access site through all these interventions until hemostasis and CFA patency is assured. Predictors of large-bore access closure failure include obesity, thoracic aneurysm repair, CFA calcification, CFA depth >4 cm, and sheath size >20 F, ruptured indication, female sex, and coronary artery disease (Table 52.2).⁷⁷

StarClose

The StarClose VCD delivers a nitinol clip to close the access site. A randomized prospective study comparing StarClose to manual compression showed no difference in complications. The results of the diagnostic StarClose cohort have been reported separately. Results for the interventional arm revealed major vascular complications occurring in 1.1% of StarClose subjects and 1.1% in manual compression subjects ($P = 1.00$). No infections were seen in either cohort. Minor complications in the StarClose interventional group occurred at a rate of 4.3% and with compression at 9.9% ($P = 0.107$). Procedural success ranges from 93.9% to 100%.^{78–80}

Exoseal

Exoseal is a percutaneous vascular closure system based on an extravascular, bioabsorbable polyglycolic plug and comes in a 5-F device. A large retrospective review showed that immediate hemostasis was achieved in 93.9%. Difficulty with deployment was attributable to malfunctioning of the device, massive

TABLE 52.2 Risk Factors for “Perclose” failure⁵⁴

Obesity
Thoracic aneurysm repair
Access calcification
Access depth >4 cm
Large sheath size (>20 F)

vascular wall calcifications, postoperative scar tissue, or too steep a puncture angle. Minor complications were observed in 7.4% with PSA (1%), inguinal hematomas (6.3%), and stenosis (0.1%).⁸¹ Boschewitz et al. demonstrated a 98% technical success rate with no major complications and a 0.7% minor complication rate.⁸² A prospective analysis comparing Exoseal to manual compression showed no device failures and no major complications in the Exoseal group. Patient pain scores and satisfaction were higher with Exoseal than manual compression.⁸³

Angio-Seal

Angio-Seal (St. Jude Medical, St. Paul, MN) is a collagen plug closure device. Its use has been associated with less time to hemostasis and earlier ambulation compared to manual compression. The Angio-Seal device has been associated with ischemic complications when the device is deployed incorrectly.^{84–88} However, the overall major complication rates are similar to other devices.^{89,90}

Mynxgrip (Mynx)

The Mynxgrip (Mynx) closure device (Cordis, Milpitas, CA) creates an immediate seal through the delivery of a polyethylene glycol plug external to the arteriotomy at the sheath

access point. The sealant expands as red blood cells and platelets enter its porous membranes, further covering the access site, and within 30 days, the sealant is dissolved completely by hydrolysis, leaving no intravascular or foreign substances behind. In a registry report including 73,124 patients who had received Mynx devices after PCI procedures with femoral access from January 1, 2011, to September 30, 2013, the Mynx device was associated with a significantly greater risk of any vascular complication than alternative vascular-closure devices (absolute risk, 1.2% vs. 0.8%; relative risk, 1.59; 95% confidence interval [CI], 1.42 to 1.78; $P < 0.001$); there was also a significantly greater risk of access-site bleeding (absolute risk, 0.4% vs. 0.3%; relative risk, 1.34; 95% CI, 1.10 to 1.62; $P = 0.001$) and transfusion (absolute risk, 1.8% vs. 1.5%; relative risk, 1.23; 95% CI, 1.13 to 1.34; $P < 0.001$).⁹¹

BLEEDING COMPLICATIONS

The most common complication of VCD is device failure resulting in bleeding. For the Perclose Proglide, a wire can be replaced through the barrel of the device to permit replacement of a sheath or the use of another closure device. This allows time for normalization of the ACT, and removal with manual compression. However, if salvage of the sheath is not possible, adjunctive manual compression is required immediately. Protamine can also be given at this time to help facilitate hemostasis.

ISCHEMIC COMPLICATIONS

Less commonly, VCD malfunction can result in lower limb ischemia (Fig. 52.8). Either signs of ischemia develop immediately, or new-onset claudication or pain at rest may arise later. It is therefore prudent to obtain a baseline pulse and Doppler evaluation before an endovascular intervention and then recheck both lower extremities immediately after the procedure. The etiology of these adverse events is dependent on the device. On exploration, suture-mediated VCDs may have disrupted the back wall intima and caused an occlusive dissection flap that resulted in thrombosis. For the collagen or hydrogel matrix plug VCDs, ischemic complications occur when the prothrombotic material is inadvertently advanced through the arteriotomy, which can potentially embolize or cause local thrombosis. Treatment options for these complications include groin exploration with standard surgical thrombectomy, primary repair, or bypass.

PROCEDURE-SPECIFIC COMPLICATIONS

All endovascular procedures are dependent on the use of a combination of wires, catheters, sheaths, balloons, stents, and interventional devices. Complications caused by these devices can potentially be limb- or life-threatening, but in many cases, they can be treated with adjunctive endovascular interventions. For a safe and successful intervention, it is critical that high-risk vessels be identified on either preoperative imaging

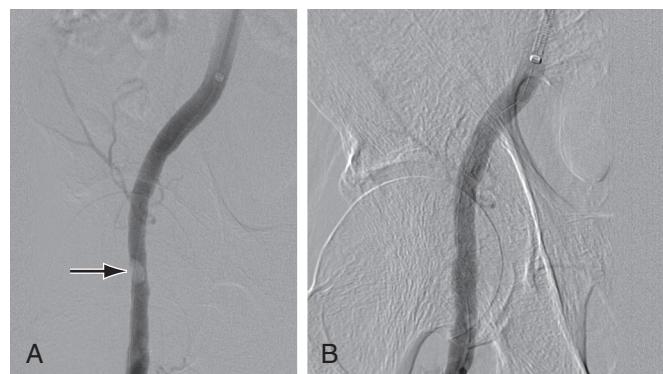


Figure 52.8 (A) Maldeployment of a vascular closure device causing arterial occlusion (arrow). (B) Successful treatment of occlusion with atherectomy.

or initial angiography. This may prompt earlier anticoagulation, use of protection devices, or use of smaller catheters and sheaths to prevent adverse outcomes.

Dissection

Balloon Angioplasty Dissection

One of the more commonly encountered problems during percutaneous procedures is intimal/medial dissection. This has been reported up to 7% of the time after balloon angioplasty.⁹² Balloon angioplasty of atherosclerotic vessels almost always results in intimal dissection. Balloon inflation causes stretching and disruption of the plaque and overlying intima that results in a tear or dissection. Pulsatile arterial flow can then propagate the dissection distally and result in flow-limiting obstruction or arterial occlusion. Arteriography depicts the typical luminal flap appearance with contrast media present on both sides of the dissection. Overdistension of a balloon in a normal vessel can also result in dissection. Postangioplasty dissections are initially treated by sustained inflation of a low-pressure angioplasty balloon in an attempt to “tack down” the dissection flap. If low-pressure angioplasty is unsuccessful and there is still a significant (>30% or flow-limiting) dissection, a self-expandable or balloon-expandable stent may be used to repair the dissection. Theoretically, the stent tacks the intima, increases the luminal diameter, and prevents further propagation of the dissection flap. Focal dissections in the infrainguinal vessels can also be treated by excision with a directional atherectomy device. If there is any question that a wire, catheter, or device is subintimal, the procedure should be halted and a low-profile catheter advanced to the point of resistance. If blood cannot be aspirated from the catheter, it is probably subintimal and should be withdrawn until blood can be aspirated. Low-pressure hand injection can then be performed. A subintimal position will be demonstrated by contrast material stagnating within the dissection plane without washout. Small dissection planes that have been created in normal, nondiseased arterial segments, especially in large-caliber arteries such as the iliac arteries, can be tolerated if there has been no narrowing of the lumen and no evidence of thrombus development, particularly if the dissection is retrograde to the flow of blood. Alternatively, large iatrogenic dissections with a high probability of occluding

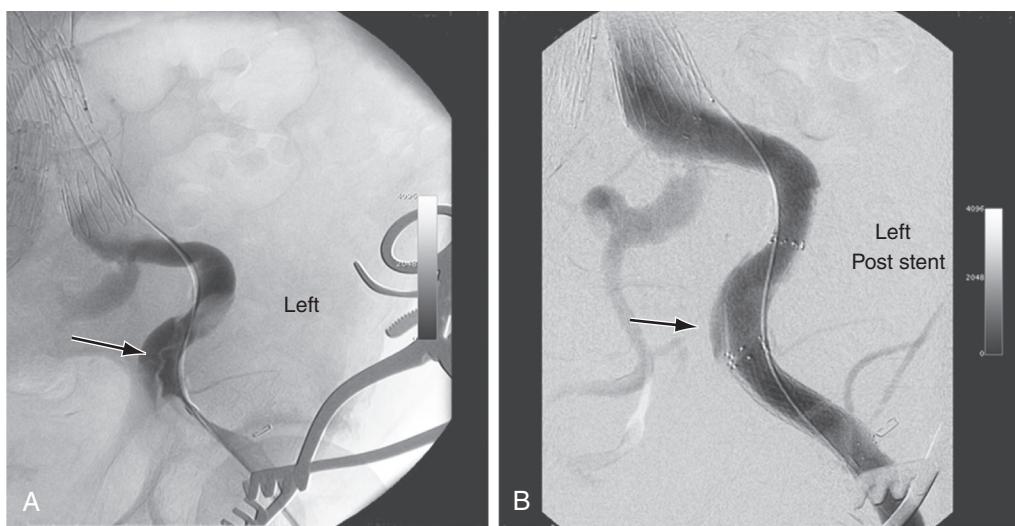


Figure 52.9 (A) Arterial dissection causing occlusion. (B) Successful treatment of occlusion with stent.

the vessel or thrombosing require intervention (Fig. 52.9) (see Ch. 111, Aortoiliac Disease: Endovascular Treatment and Ch. 113, Infrainguinal Disease: Endovascular Therapy).

Subintimal Angioplasty

In certain circumstances, such as crossing chronic total occlusions, creation of a dissection plane and subintimal advancement are done intentionally. It is critical that the point of reconstitution distal to the chronic total occlusion be exactly identified and the wire not be allowed to traverse more than 1 or 2 cm beyond the reconstitution point while in the subintimal plane. If accessing the native lumen is difficult, reentry devices such as the Outback catheter (Cordis, Johnson and Johnson, New Brunswick, NJ) can be used.^{93,94} This has been associated with a low complication rate.

Embolization

Embolization can be a devastating complication of endovascular procedures. It can transform a relatively straightforward procedure performed for claudication into a complex high-risk limb salvage endeavor (Fig. 52.10). In patients with large-volume atheromatous disease, any wire, catheter, or sheath manipulation can result in distal embolization. Catheter movement across friable thrombus or atheromatous plaque, especially in aneurysmal vessels or a diseased aortic arch, can liberate embolic debris. Depending on location, this can result in “trashing” of runoff vessels, and if in the aortic arch, it can lead to stroke. The rates of lower extremity embolism have been reported from 1%–3.8%, although not all are clinically significant if there is alternate distal flow. Atherectomy devices have been associated with higher rate of distal embolization.⁹⁵ Also, presence of thrombus in the lesion and TASC C and D lesions have also been shown to be associated with embolization.^{95,96}

Management

Prevention of distal embolization is best achieved by recognition of high-risk vessels on preintervention imaging. It is then



Figure 52.10 Distal embolization after proximal endovascular intervention.

prudent to institute anticoagulation early and minimize manipulation across the lesion. Moreover, some groups have used embolic protection devices in lower extremity interventions by extrapolation from the carotid angioplasty and stenting experience, especially in the setting of large-volume plaque burden, significant thrombus burden or single-vessel runoff.⁹⁷ If embolization does occur, endovascular rescue can be implemented for salvage of the vessel. First, the patient should be heparinized with confirmation of adequate anticoagulation by the ACT, and if needed, additional heparin should be administered. Aspiration catheters (Export catheter, Medtronic, Minneapolis,

MN; Pronto catheter, Vascular Solutions, Inc., Minneapolis, MN) can then be used to remove obstructing thrombus or free-floating plaque.⁹⁸ Percutaneous embolectomy is another option that has demonstrated favorable results with acute embolic occlusions or AngioJet (Possis Medical, Minneapolis, MN) can be used to diminish thrombus burden in the event of distal embolization. The Penumbra device is a newer thromboaspiration device that is being increasingly used in the periphery for embolectomy or thrombectomy and comes in a wide range of sizes.^{99–101} Finally, thrombolytic agents can be administered as an adjunct to the aforementioned maneuvers to dissolve potential thrombotic emboli or if there is concern for possible *in situ* thrombosis after an embolus has occurred. If these techniques are unsuccessful and the patient has signs of acute ischemia, standard open surgical techniques are warranted, including open thromboembolectomy and, if necessary, surgical bypass.

Perforation

Wire Perforation

Isolated wire perforations, especially in lower extremity vessels, usually seal with conservative management (Fig. 52.11). Stiffer wires have a higher propensity to perforate and should therefore be avoided as an initial navigation wire or in small, highly diseased vessels. Wires that have perforated a vessel can often be seen on fluoroscopy as traveling outside the normal course of the artery, and the tip of the wire will curl abnormally as it enters the soft tissue planes. Once the wire is removed, angiography may reveal extravasation of contrast material. Recognition of this problem is essential before advancing catheters or devices, and the wire should be withdrawn and an attempt made to find a new subintimal plane to traverse the lesion.

When performing interventions on the visceral arteries, wire advancement can lead to perforation of the end organ. For example, renal angioplasty requires positioning of a stiff wire in the distal renal artery to allow placement of a sheath and eventual angioplasty and stenting. In rare circumstances, the wire is advanced too far distally and can potentially perforate an intra-parenchymal vessel or the kidney capsule itself. Such perforation inevitably results in trauma to the kidney with subsequent hemorrhage into the retroperitoneum (Fig. 52.12). Treatment of this complication depends on the patient's clinical status (see Ch. 129, Renovascular Disease: Endovascular Treatment).

Angioplasty Perforation

Perforation secondary to angioplasty can result in life-threatening bleeding, especially in atherosclerotic vessels. Over-distension of a calcified vessel that has lost its elastic compliance can result in disruption of all layers of the arterial wall and frank perforation. For iliac lesions, perforation can potentially cause massive hemorrhage into the retroperitoneum. Angiography will delineate the extent of rupture based on extravasation of contrast material (Fig. 52.13). Once the perforation is identified, a large compliant balloon should be placed across the injured segment and gently inflated until it tamponades the bleeding site. A covered stent can be used for repair, although sometimes open repair is required.^{102,103} For aortic bifurcation

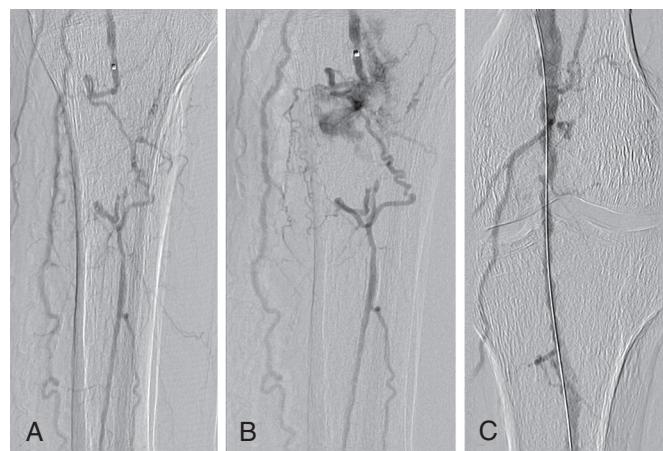


Figure 52.11 Wire perforation after attempted subintimal recanalization. (A) Before attempting to cross occlusion. (B) Wire perforation of vessel. (C) Successful recanalization.

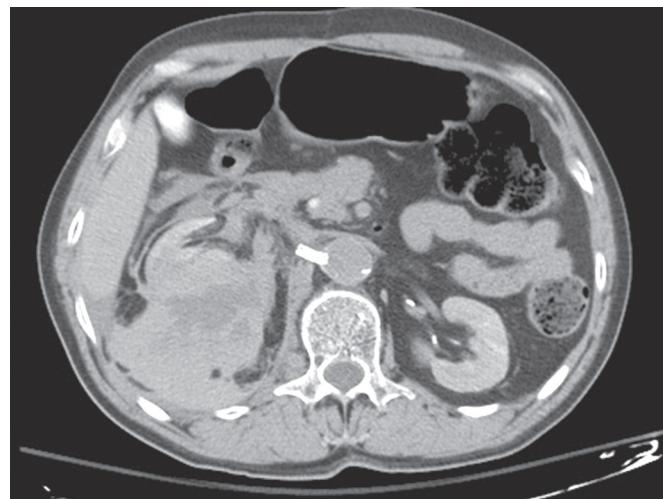


Figure 52.12 Right kidney iatrogenic perforation.



Figure 52.13 Retroperitoneal hemorrhage as seen by extravasation of contrast material.

lesions or proximal iliac perforation, aortic stent-grafting or aorto-uni-iliac with femoro-femoral bypass may be an option. If endovascular repair is not an alternative, the occluding balloon can be left in place while the patient is prepared for open surgical repair.

Angioplasty-induced rupture of the infrainguinal vessels is rarely a life-threatening condition; however, it can result in PSA formation or arterial occlusion. In a study by Hayes and colleagues, 1409 patients undergoing peripheral angioplasty were evaluated and 52 (3.7%) had suffered arterial perforation.¹⁰⁴ Risk factors for perforation included advanced age, diabetes, and subintimal angioplasty. There was no mortality, no patients required surgery at the site of perforation, and 27 of the 52 procedures were completed successfully despite the complication.

Atherectomy Perforation

Atherectomy devices, when allowed to excise too deeply, can result in arterial perforation. Generally, this is a rare phenomenon that occurs in less than 1% of cases.¹⁰⁵ Oversizing of the device and use near bifurcations can also result in perforation. Prevention of this injury rests on knowing the level of excision within the arterial wall. It is also useful to image the artery orthogonally; multiple views facilitate localization of the device relative to the arterial wall. Intravascular ultrasound can also be performed to determine the depth of plaque excision. Use in heavily diseased arteries with multiple passes along one plane causes an asymmetric excision that can thin the wall down to the subadventitial space. This places the vessel at high risk for the development of an acute or subacute AVF and, in rare cases, PSA formation.

Atherectomy-induced AVF is characterized on angiography by rapid venous filling and, with large AVFs, by diminished or abolished distal arterial outflow (Fig. 52.14). With involvement of the SFA, the majority of fistulae are of no clinical significance and will thrombose spontaneously. If, however, the fistula causes compromised distal perfusion, treatment is warranted. Initial treatment is prolonged low-pressure balloon inflation. If this is unsuccessful, reversal of the anticoagulation is indicated, and if this fails, placement of a covered stent is an option. Under conditions of worsened ischemia that can be attributable to the fistula, surgery may be required if endovascular maneuvers fail. Surgical options include ligation of the vein above and below the site of the fistula or, if necessary, bypass.

Endovascular Aneurysm Repair Access Site

Stent-graft implantation for the abdominal or thoracic aorta requires the use of large (18- to 24-F) sheaths for delivery of the device (see Ch. 74, Endovascular Aneurysm Repair Techniques). Proper preoperative assessment of access site vessels, including the femoral and iliac arteries, is a requirement for safe deployment of these grafts. Despite appropriate planning, however, iliac tortuosity, vessel diameter, atherosclerotic disease, and calcification can be limiting factors. In a single center review of EVAR cases, the incidence of arterial rupture was 3%, with the common iliac artery being most affected. More

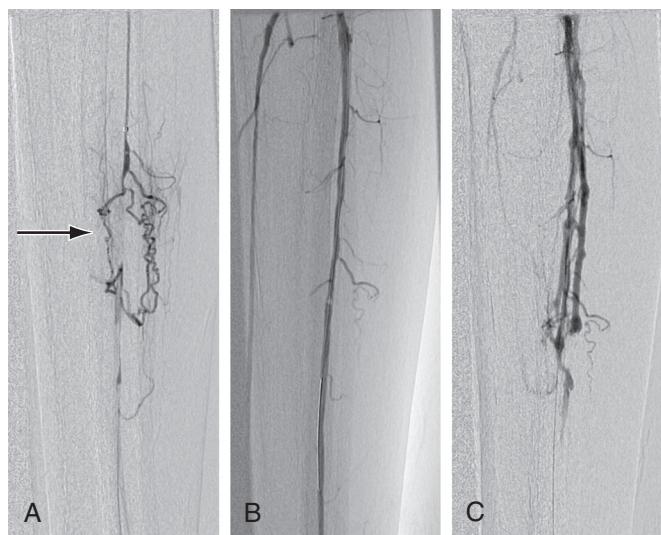


Figure 52.14 Atherectomy-induced arteriovenous fistula characterized on angiography by rapid venous filling. (A) Before attempting to cross occlusion. (B) Successful recanalization. (C) Delayed filling showing arteriovenous fistula.

than half of the patients became hypotensive after the rupture. The majority were repaired in endovascular fashion, although 25% required open repair. There were no intraoperative deaths, although the postoperative mortality rate was 20%.¹⁰⁶ Fernandez et al. analyzed rates with both EVAR and TEVAR, and reported that iliac artery rupture was more likely to occur during TEVAR (8.9%) than EVAR (2.98%), and in women. Patients in the ruptured group experienced longer lengths of stay and a higher procedure-related mortality.¹⁰⁷

With evolving experience with these devices, many investigators have instituted a lower threshold for using an iliofemoral or iliac artery conduit to gain larger, more proximal access, although this has been shown to increase perioperative morbidity and mortality.¹⁰⁸ Despite even the most diligent preparation, rupture of the access vessels can occur, and operators should be prepared to manage this devastating complication by having appropriately sized balloons and covered stents immediately available in the area where the aortic stent-graft surgery is being performed. Most ruptures are detected at the conclusion of the procedure when the sheaths are being removed from the iliac/femoral vessel. Before removal of the sheath, the sheath itself is occluding the ruptured iliac vessel. The patient will not begin to hemorrhage from the perforation until the sheath is removed. Ruptured iliac vessels will usually cause acute and profound hypotension. It is crucial that wire access be maintained to allow placement of an occlusion balloon in all cases until it is proved that the patient is hemodynamically stable after removal of the sheath. In extreme cases, operators may encounter the “iliac artery on a stick,” in which an everted cast of the iliac artery is stuck to the sheath and avulsed on removal of the sheath (Fig. 52.15). Definitive treatment of this adverse event can be accomplished by placing multiple covered stents that span the area of rupture. At any time, however, surgical repair may be required to repair an injury that has not completely sealed or was not amenable to stent coverage.

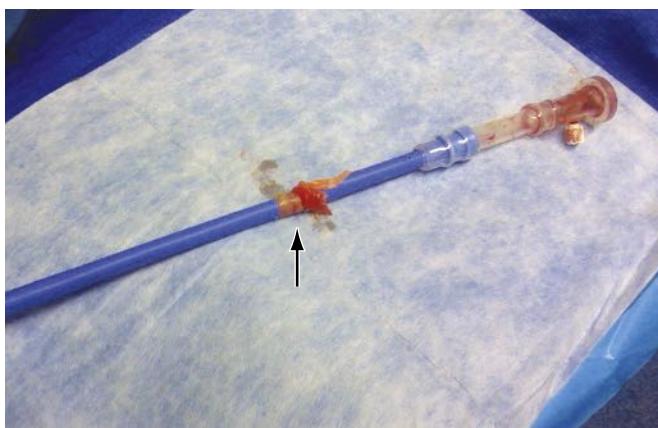


Figure 52.15 “Iliac artery on a stick” – an everted cast of the iliac artery is stuck to the sheath and avulsed on removal of the sheath.

OTHER ENDOVASCULAR PROCEDURE COMPLICATIONS

Thrombolytic Therapy Complications

Catheter-directed thrombolysis has become the first line of treatment at many institutions for extensive deep venous thrombosis, acute arterial ischemia, and pulmonary embolism.^{109–111} In two clinical trials comparing surgery and thrombolysis (TOPAS [Thrombolysis or Peripheral Arterial Surgery] and STILE [Surgery vs. Thrombolysis for Ischemia of the Lower Extremity]), the life-threatening hemorrhage rates were 13% and 5.6%, respectively.^{112,113} The most common complication is a hematoma at the access site.¹¹⁴ Intracranial hemorrhage has been reported 0.7% of the time and gastrointestinal hemorrhage 1.6% of cases.¹¹⁵ Treatment of minor bleeding is primarily application of continuous pressure locally. Patients receiving thrombolytic therapy should be monitored by serial hematocrit determination and coagulation studies. Lower doses of lytic agents may lead to fewer complications.¹¹⁶ A profound decline in fibrinogen levels (<150 mg/dL) should at the minimum raise concern for increased bleeding risk. A drop in hematocrit, especially with hemodynamic instability, should prompt concern for retroperitoneal hemorrhage, and a CT scan should be obtained. If the bleeding is significant and requires transfusion, lytic treatment should be halted. Similarly, a change in mental status should prompt stoppage of thrombolytic therapy given the risk for intracerebral bleeding, and imaging of the brain with either CT or magnetic resonance imaging should be performed (see Ch. 43, Thrombolytic Agents).

Device Infection

Stents and Endovascular Stent Grafts

Infection of EVAR and TEVAR grafts are rare but potentially devastating complications. The reported incidence ranges from 0.6%–0.77%^{117,118} (see Ch. 75, Aortoiliac Aneurysms: Endovascular Treatment). Infection of bare-metal stents is also a rare complication of endovascular interventions. These have been

reported more in non-coronary rather than coronary stents.¹¹⁹ PET-CT has been helpful at identifying stent infections. Breaks in sterile technique, occult glove perforation, inadequate skin preparation, repeat puncture of the same arterial access site, prolonged use or reuse of an indwelling catheter, increased procedure time, puncture site hematoma, other sources of coincident bacteremia, and nonsterile angiography suites may contribute to this, but there is no clear data.¹²⁰ There have been reports of stent-graft preservation with antibiotic therapy.^{121,122}

Patients with stent infections often have clinical signs of bacteremia consisting of fever, chills, and rigors, and this should prompt a standard evaluation for other sources of infection. Once these are ruled out, stent infection should be considered, but the rarity of this complication makes it a diagnosis of exclusion. *S. aureus* is the most common organism isolated in cases of stent infection.¹¹⁹ Imaging modalities that are helpful in making the diagnosis include CT, angiography, duplex ultrasonography, and tagged white blood cell scans. Treatment should be aggressive and consist of removal of the stent and all surrounding infected tissue, which often includes a large portion of the artery. The principles of management of prosthetic graft infection should be applied in this case. Therefore, most patients require bypass with autogenous conduit or extra-anatomic reconstruction with prosthetic material. Definitive preventive measures for stent infections are unknown at this time.

Device Fracture or Embolization

Device or instrument malfunction may be encountered in clinical practice. For example, wires, catheters, or sheaths can break and leave residual, free-floating fragments within the arterial lumen. This necessitates prompt retrieval to avoid distal embolization or arterial thrombosis. The most common technique used to retrieve foreign bodies within the vasculature involves the use of endovascular snares or biopsy forceps. If a broken wire is positioned within a sheath, it is also possible to advance a balloon alongside the wire, inflate it, and drag the wire to the origin of the sheath. This technique can also be used to retrieve broken sheaths.¹²³

Improper sizing of the vessel lumen can cause a mismatch between the stent diameter and the size of the vessel. If the stent is too small, it can migrate distally and essentially embolize and lodge at a branch point or a smaller portion of the vessel. Inadvertent displacement of a stent can occur during passage of the device. For example, in patients with iliac disease that has been stented in the past, passage of the device through these iliac vessels risks stent dislodgement and embolization. Balloon-expandable stents should be advanced through the stenotic area in the sheath to avoid dislodging the stent from the balloon.

Venous Procedures

Angioplasty and Stenting

Venous angioplasty with stenting is commonly performed in patients with central venous stenosis. Vein rupture with aggressive angioplasty may occur in the setting of highly scarred or

chronically occluded vessels. Generally, vein perforations can be managed conservatively because the low-pressure system allows the injury to seal spontaneously with manual compression therapy alone.

Venous stent migration has been reported, and in the most severe cases these stents can embolize to the heart. This has been reported in the setting of iliac vein stenting, superior vena cava (SVC) syndrome, and stenting of the renal vein for nutcracker syndrome.^{124–126} Retrieval of migrated venous stents can usually be accomplished with snares; however, in some instances an operation is required for stent removal.

Inferior Vena Cava Filter Complications

Inferior vena cava (IVC) filter placement complications are rare.¹²⁷ Procedure-related complications can occur either in the acute period or months to years later. Late filter complications carry the highest morbidity and mortality rates for filters and include embolization, vessel penetration, and thrombosis of the filter.^{128–133} Embolization of the filter or filter struts can go into the heart or the pulmonary arteries and can potentially induce fatal arrhythmias.^{128,129} Embolization or dislodgement can also occur during either internal jugular or lower extremity venous catheter exchange (Fig. 52.16). Long term, in rare instances, the barbs on the filter erode through the IVC, and although most cases are asymptomatic, penetration into adjacent structures such as the duodenum, aorta or vertebral bodies can occur (Fig. 52.17).¹³⁰ The duration of filter placement is associated with the risks of penetration. Treatment of bowel perforation involves open removal of the filter and repair of the intestinal injury and the caval wall.¹³¹ The development of thrombus at the level of the filter may cause complete occlusion of the IVC with resultant venous obstructive complications, including phlegmasia, recurrent deep venous thrombosis, and postphlebitic syndrome.¹³² IVC filter occlusion has

been associated with pulmonary embolism that has failed anticoagulation as an indication for placement.¹³³ Filter fracture and embolization may occur. These complications should be considered when planning filter placement in young individuals and provides justification for the placement of temporary filters (see Ch. 153, Vena Cava Interruption).

COVID-19 Considerations

Hypercoagulability among some patients with COVID-19 may predispose to higher rates of arterial and venous thromboses complicating endovascular procedures.^{134,135} Increased central line placement by nontraditional teams has also been associated with iatrogenic injuries requiring repair.¹³⁶

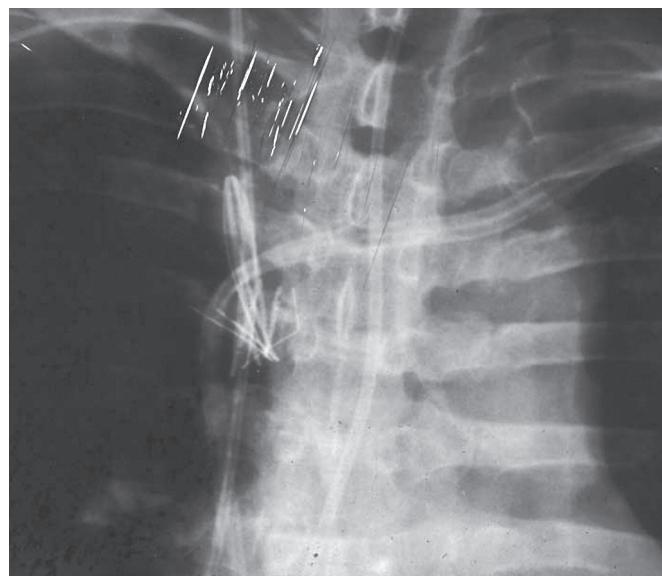


Figure 52.16 Dislodged inferior vena cava filter.

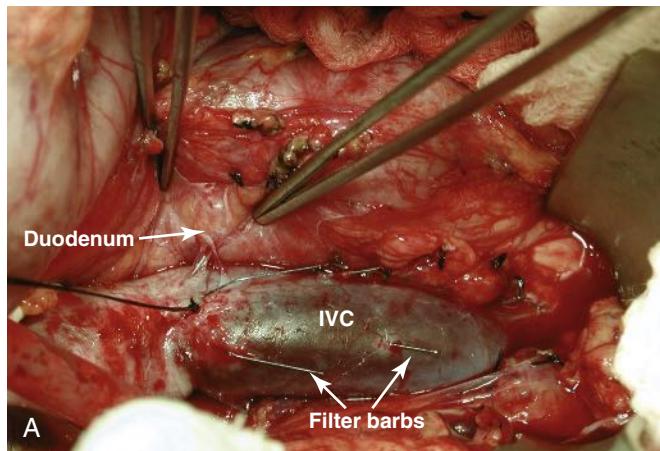


Figure 52.17 Protrusion of prongs of IVC filter into adjacent structures. (A) Bowel. (B) Spine. *IVC*, inferior vena cava.

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Venous Complications

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INCIDENCE OF VENOUS COMPLICATIONS	677
DIRECT VENOUS INJURY	677
Diagnostic Evaluation of Direct Venous Injury	678
Management of Direct Venous Injury	678
Arteriovenous Fistulas	679
Venous Thrombosis	679
COMPLICATIONS FROM VENOUS ENDOVASCULAR INTERVENTIONS	679
Diagnostic Evaluation of Complications from Venous Endovascular Interventions	681

Management of Complications from Venous Endovascular Interventions	681
INFERIOR VENA CAVA FILTER COMPLICATIONS	681
Diagnostic Evaluation of Inferior Vena Cava Filter Complications	681
Management of Inferior Vena Cava Filter Complications	681
CONCLUSIONS	683
CHAPTER ALGORITHM	684

In vascular surgery, venous complications arise from different mechanisms, ranging from traumatic to iatrogenic injury, both directly and indirectly. Complications may present as bleeding and hematoma immediately after venous injury or as occult thrombosis or fistula detected only after many months following the initial procedure. Presentations of venous complications are highly variable and can range from subtle to life-threatening. In general, the greater the severity of the clinical presentation of the venous complication, the greater the magnitude of the treatment required, and because of this, treatment options can be controversial.

INCIDENCE OF VENOUS COMPLICATIONS

The most common venous complication after any type of surgery or illness is deep venous thrombosis (DVT) (see Ch. 146, Acute Deep Venous Thrombosis: Epidemiology and Natural History and Ch. 148, Acute Lower Extremity Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment). Although not necessarily a direct venous injury, the incidence of DVT after vascular surgery has been reported as high as 20%.¹ The incidence of DVT after venous puncture is not widely reported but was found to be up to 60% without anti-coagulation during cardiac procedures² and in 36% of patients with an existing clot who received an inferior vena cava (IVC) filter.³

Direct venous injury requiring dedicated repair is most commonly seen in trauma patients and as a procedural complication. These injuries can lead to bleeding, thrombosis or, more rarely, arteriovenous fistula (AVF). Venous injury in trauma has been reported as high as 28% of penetrating wounds and is usually associated with arterial injury.⁴ Iatrogenic injuries during other surgeries are rarely reported, but the Mayo clinic described 44 injuries during major abdominal surgery over 17 years. Average blood loss from these injuries was nearly 4L, and there was an 18% mortality rate.⁵

DIRECT VENOUS INJURY

Direct venous injury involves trauma to a vein. The expanding field of endovascular therapy for the treatment of vascular disease has steadily increased the number of access site procedural complications, both arterial and venous (see Ch. 52, Local Endovascular Complications and their Management). Since 1995, there has been approximately a 10-fold increase in the rate of peripheral vascular interventions.⁶ Access site complications occur in 1.0% to 11% of these procedures.^{7–10} Central line placement can also cause direct injury to the vessels. Injury can be apparent on physical exam, but hypotension after a percutaneous intervention should always include the differential diagnosis of a remote hematoma. After femoral interventions, an acute drop in hemoglobin level and lower abdominal/flank pain should raise suspicion for a retroperitoneal hematoma.

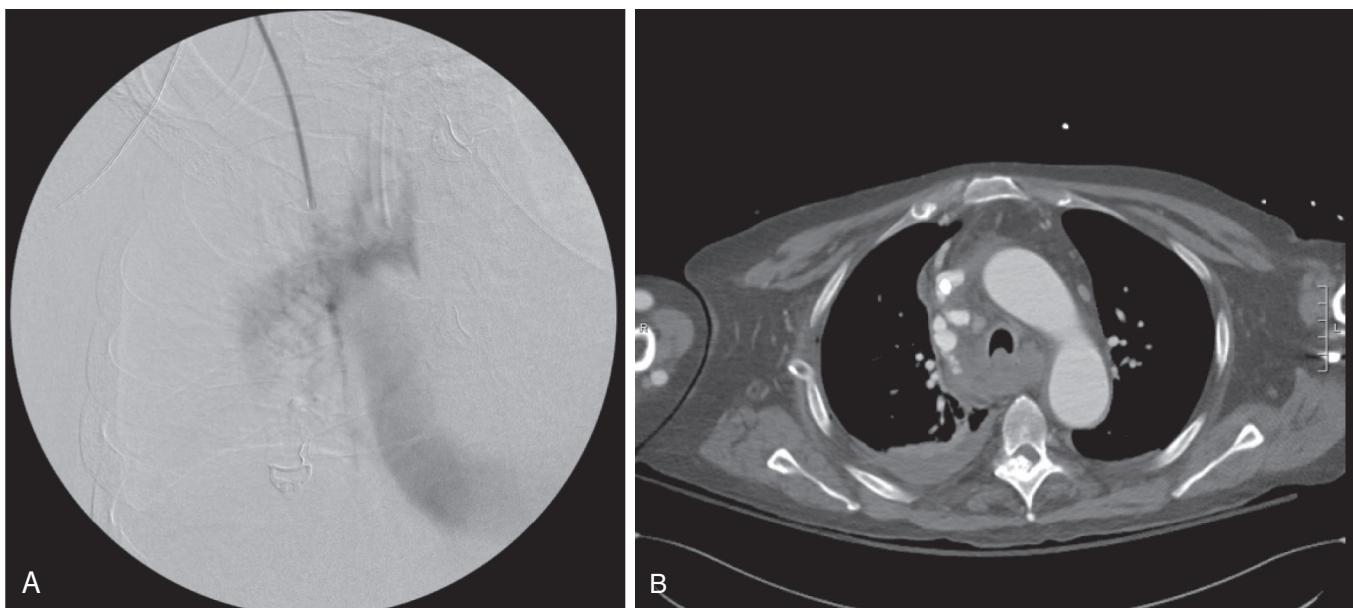


Figure 53.1 (A) Venogram demonstrating extravasation after attempted recanalization. (B) CT scan demonstrating mediastinal hematoma after attempted recanalization.

Isolated venous injury during dissection of the adjacent arterial or nerve structures or other surgical exposures often goes unreported. Injuries are commonly repaired primarily, or the affected veins may be ligated, relying on collateral circulation. Direct venous injuries are often only diagnosed and reported when a life-threatening hemorrhage or hemodynamic instability occurs (Fig. 53.1).

The risk of direct venous injury can be minimized by proper technique and recognition of high-risk patients. Predictors of groin complications from any vascular access have been well described. Obesity, large sheath size, previous catheterization, and anticoagulation are notable risk factors for all access site complications.¹¹ For percutaneous interventions, including central line placements, ultrasound guidance and the Seldinger technique are considered standard of care procedural steps.^{12,13}

Diagnostic Evaluation of Direct Venous Injury

During percutaneous interventions, a hematoma is most indicative of a complication from a venous injury. A hematoma may present as obvious swelling, but other more subtle signs and symptoms include access site pain, skin ecchymosis, continued bleeding through the puncture site, and hypotension. Duplex ultrasound of the localized hematoma is often necessary, especially if the hematoma is pulsatile, has a bruit over it, or is exquisitely tender, in order to rule out arterial pseudoaneurysm or AVF. Venous extravasation is generally not seen on ultrasound, but is instead seen as hematoma. Venous compression or thrombosis from the hematoma can also be seen.

A retroperitoneal hematoma is a clinical diagnosis. Retroperitoneal hematomas from femoral venous accesses have subtle physical exam findings but may convey a risk of morbidity and mortality if not identified. The retroperitoneal space accommodates a large amount of blood without tamponade from surrounding structures, and thus, complaints of back or

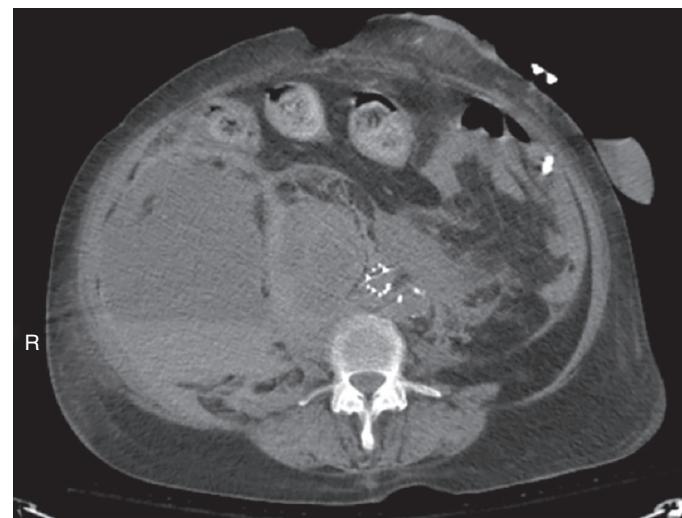


Figure 53.2 Large Retroperitoneal Hematoma. Note the indistinct border of the inferior vena cava (IVC). This patient had an IVC filter placed shortly before this scan.

lower abdominal pain, hypotension, tachycardia, and oliguria should raise suspicion to diagnose and manage urgently. Patients should promptly be considered for a CT scan. By using contrast, an abdominal and pelvic CT scan can readily identify arterial or venous injury and resulting hematoma, pseudoaneurysm, or extravasation (Fig. 53.2).

Venous injuries during open surgical approaches are often diagnosed by direct visualization. However, if clinically occult, computed tomography and magnetic resonance angiography in the delayed phase can provide a diagnosis.

Management of Direct Venous Injury

Venous access site injury during a percutaneous intervention often results in hematoma formation. Early recognition limits

significant morbidity. Although often self-limiting, pressure over the puncture site is recommended. The area should be marked to evaluate for any expansion and be serially monitored. Monitoring serial hemoglobin levels and prolonging bedrest is recommended. Most hematomas resolve within a few weeks. Hematoma size varies, and if skin compromise is evident, evacuation and debridement of the affected area is necessary.

In coagulopathic patients, however, aggressive resuscitation with blood products may be required, especially if a retroperitoneal hematoma is suspected. Although most retroperitoneal hematomas can be managed with resuscitation, bedrest, and monitoring serial hematocrit levels, hemodynamic instability, ongoing blood loss, and neurologic deficits due to compression of adjacent nerves are indications for further imaging and possibly open surgical exploration or endovascular treatment. Complications from venous intervention remote from the access area are now recognized as increasingly common. Treatment of these complications is an evolving area of vascular surgery and is individually determined on a symptomatic basis. With larger covered stents now available, the capability of placing these in the central veins exists, and may be a safer option than open repair, especially in patients with significant comorbidities.

Venous injury during open surgical procedures, such as an iliac vein injury during an aortobifemoral bypass or spine exposure, ranges from small adventitial hematomas to complete transections. Small injuries often are managed conservatively with direct pressure. However, tears and lacerations can be repaired with 5-0, 6-0, or 7-0 monofilament sutures as appropriate for vein size. Proximal and distal control is often not necessary but can be done gently with sponge sticks if required. Encircling and clamping veins to assist in repairing injuries frequently causes additional trauma and bleeding as small branches may be sheared and large soft veins are susceptible to clamp trauma. In general, when severely injured and resulting in hemodynamic instability, the brachiocephalic, internal jugular, subclavian, and extremity veins can be ligated, especially if the contralateral side is patent. Open repair, however, is generally preferred. Vena caval, femoral, brachiocephalic, or subclavian/axillary vein injuries can be closed with a transverse primary repair with 4-0 or 5-0 monofilament suture if there is no significant loss of vein caliber. With a loss of caliber, it is necessary to replace this lost segment, usually with lateral venorrhaphy and a bovine pericardial patch in the IVC or vein patch in smaller vessels, to avoid tension or stricture. Large abdominal veins such as the renal or superior mesenteric veins should be repaired. However, in the context of hemodynamic instability, vein ligation may be indicated.

For vena caval injuries, endovascular repair options include balloon occlusion or control, and the use of a covered stent. These interventions are usually performed in a hybrid OR. Balloon occlusion with large, low-pressure balloons from above and below the injury, either inserted percutaneously from the jugular and femoral sites or inserted through the injury, can slow down blood loss and may allow enough visualization for an open repair. If the injury is being managed percutaneously,

there are reports of covered stent grafts in the IVC.^{14–17} These are difficult to size, as the injured cava may have ill-defined walls and the size of the tear may be difficult to appreciate on CT or venogram. In addition, there may be spasm of the IVC or underfilling from blood loss that leads to placement of cuffs that could embolize once the cava is fully expanded.

In the event of a posterior vena caval injury, this difficult problem can possibly be managed by control of the cava and opening the cava on the anterior surface to visualize the posterior tear. This can then be repaired from inside the cava and the anterior exposure site can be primarily closed in a transverse manner. If there is a significant loss of calibre in any of these large veins, and the patient is hemodynamically stable, the injured section of vein can be replaced with a prosthetic graft, usually 20–24 mm in diameter, or a spiral vein graft if time allows. If a prosthetic graft is used, consideration should be given to prolonged systemic anticoagulation, a distal arteriovenous fistula, or both to optimize patency. Severe venous injuries, especially in the infra- or suprahepatic regions of the IVC, carry a very high morbidity and mortality.¹⁸

Arteriovenous Fistulas

An arteriovenous fistula (AVF), a direct communication between an artery and a vein, often can occur after penetrating trauma, where ongoing bleeding from an artery decompresses into an adjacent venous injury (Fig. 53.3). With increasing numbers of invasive percutaneous procedures, vascular cannulation accounts for most AVFs.¹⁹ The incidence ranges from 0.0006% to 0.88%.^{20–22} Total knee replacements, lumbar disc surgery,^{23,24} and percutaneous biopsies, such as in transplant kidneys, may also result in AVFs.

Venous Thrombosis

A DVT may manifest with varied signs and symptoms but is a particularly important clinical diagnosis to keep in mind after any venous injury or intervention. After percutaneous interventions such as IVC filter placement, compression of the punctured vein after instrumentation predisposes to thrombus formation.²⁵ Furthermore, any instrumentation or catheter placement within the vein activates the clotting cascade by virtue of the venous trauma involved (Fig. 53.4).²⁶ Surgical repair after direct injury to a vein can also be a nidus for thrombus formation (see Ch. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment and Ch. 150, Acute Upper Extremity and Catheter-Related Venous Thrombosis).

COMPLICATIONS FROM VENOUS ENDOVASCULAR INTERVENTIONS

Venous angioplasty and stenting are instrumental in salvaging hemodialysis access. Outflow and central venous stenosis are often treated with balloons and stents to improve secondary patency of hemodialysis fistulas and grafts. Left iliac vein

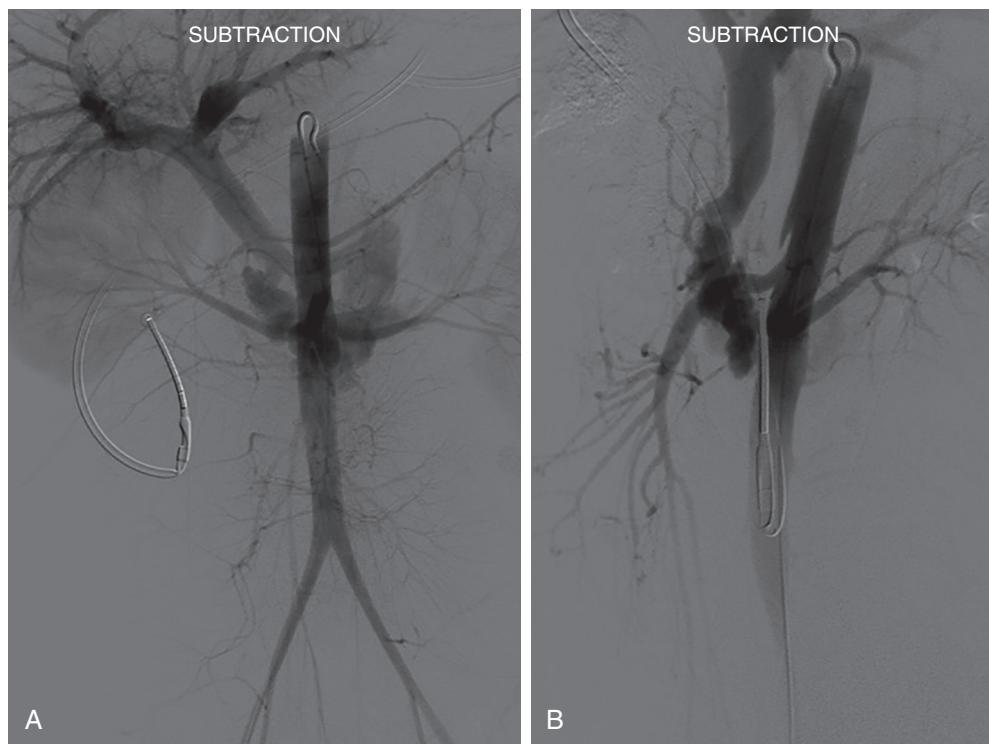


Figure 53.3 Aorto-superior mesenteric vein fistula draining into the portal vein in AP (A) and lateral (B) projections after a gunshot wound to the abdomen. Both vessels were repaired primarily. (Image courtesy Mitchell W. Cox, MD.)

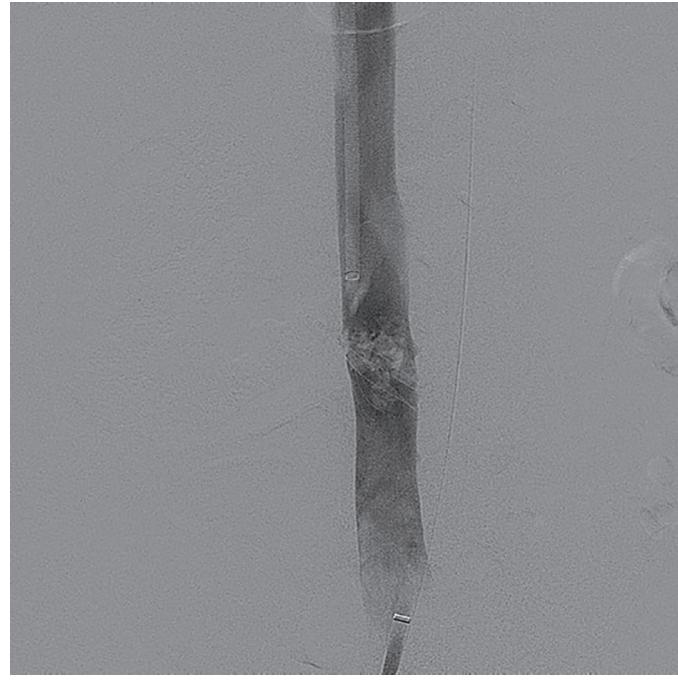


Figure 53.4 New Thrombus after Attempts to Retrieve Tilted Inferior Vena Cava Filter. Filling voids can be seen from the draining renal veins near the superior sheath tip, and new thrombus surrounds the tilted filter directly below. This thrombus occurred after prolonged attempt to remove the filter. (Image courtesy Mitchell W. Cox, MD.)

angioplasty and stenting is common in relieving left leg swelling for patients with May-Thurner and post-thrombotic syndromes. Caval recanalization and reconstruction with stents have been shown to improve venous ulcer healing.²⁷ Venous stenosis, especially within veins arterialized from hemodialysis

access, may be difficult to dilate and require high-pressure balloons. However, not infrequently, high-pressure inflations cause venous rupture (see Ch. 161, Iliocaval Venous Obstruction: Endovascular Treatment).

Migration is another potential complication of endovascular intervention and is usually associated with central vein stent deployment.²⁸ Central veins are more compliant and thus, without adequate stent oversizing, venous stents are more prone to migration. Intravascular ultrasound aids in accurately measuring the diameters of these compliant lumens intraoperatively. In addition to adequate oversizing, accurate proximal and distal positioning of the stent with adequate anchors limits migration.²⁹

Wire perforation from endovascular venous interventions is rare but can happen when recanalizing chronic occlusions, such as during iliacocal reconstructions. Stiffer wires have a higher propensity to injure the vessel and should be used cautiously. However, significant bleeding from wire perforation is uncommon, as the occluded veins have low flow.

Iliac venous stenting has entered a new era with stents designed specifically for the venous system.³⁰ As these new stents are all nitinol-based, they have a higher radial force than previously placed stainless steel stents and may increase the well-known occurrence of pain after iliac stenting. This pain is thought to arise from irritation of the genital-femoral nerve on the anterior surface of the psoas muscle which is immediately posterior to the iliac vein. Especially after recanalization of complete iliac vein occlusions, the newly expanded vein with a stiff stent exerting high radial force may result in ipsilateral flank pain radiating to the genital area. This pain can be quite severe and may last from 1–2 days to several months. It is very rarely permanent, but patients should be warned of this prior to any iliac stenting.

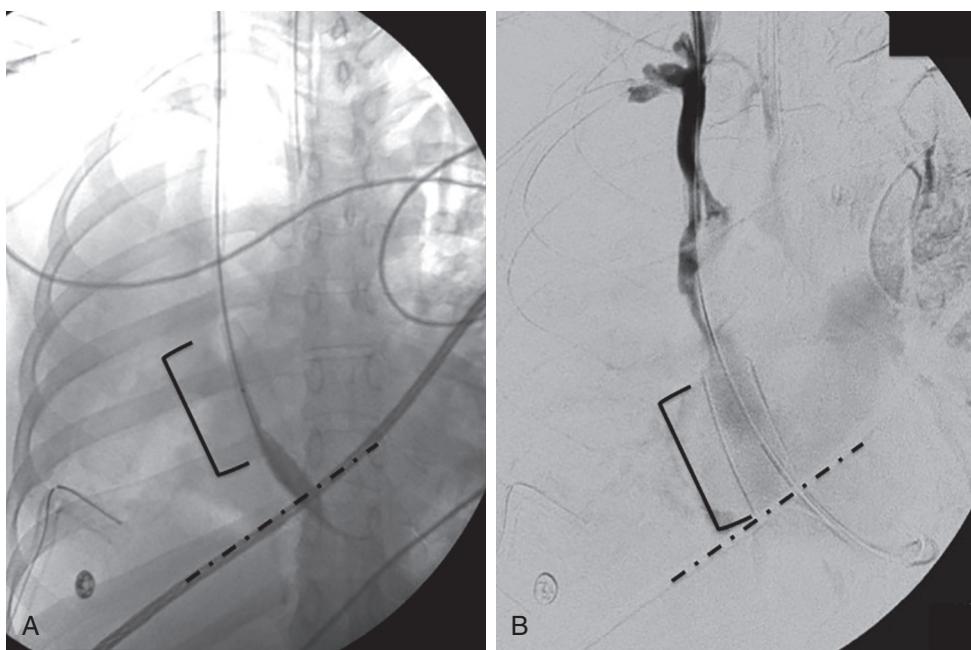


Figure 53.5 Embolization of a Stent from the Superior Vena Cava into the Right Atrium. Note the position of the stent (brackets) in relation to the fixed wire (dashed line) overlying the patient at deployment (A) and after ballooning (B).

Diagnostic Evaluation of Complications from Venous Endovascular Interventions

Most endovascular complications of venous interventions occur intraoperatively as, for example, when a venous stent “watermelon seeds” into the right side of the heart (Fig. 53.5). Therefore, diagnosis is immediate. Perforations after venous angioplasty are quite evident when a post-angioplasty image is taken and can be addressed immediately, and a hematoma may be present in the affected extremity.

Management of Complications from Venous Endovascular Interventions

Most venous ruptures are self-limiting due to the low pressure of the venous system and will seal after a brief period of balloon tamponade. A balloon slightly smaller than the surrounding venous diameter should be placed across the perforated venous segment and gently inflated to low pressure (<5 atm) for at least 5 minutes. If there is still extravasation after this maneuver is performed, a covered or even bare metal stent can be placed across the perforation to achieve hemostasis.

Migrated stents are often percutaneously retrieved with snares if they can be pulled into a large sheath. Migrated stents can also be removed through surgical cutdowns, and the venous system may need to be reconstructed.³¹

Venous embolization devices can also migrate. Coils and plugs have been found in the heart and lungs (Fig. 53.6), as the venous diameter has a large variation and may be in spasm at the time of instrumentation. Placing plugs or coils in the internal iliac veins should be done with great caution, as these can embolize.³² If this vessel needs to be coiled, the ends of the coils should be anchored in branch vessels and extended into the larger veins (Fig. 53.7).

INFERIOR VENA CAVA FILTER COMPLICATIONS

Inferior vena cava filter (IVCF) placements are performed to prevent venous thromboembolism. These filters and procedure-related complications have been well studied (see Ch. 153, Vena Cava Interruption). Misplaced IVCFs, pneumothorax, hematoma, air embolism, AVF, insertion site thrombosis, and carotid puncture are a few of the well-described procedural complications.^{33,34} Late complications include IVCF thrombosis, embolization from a thrombosed IVCF, fracture, and perforation into adjacent structures.³⁵ Migration of IVCF into the right heart carries high morbidity and mortality,³⁶ and it often occurs when the cava is too large to anchor commercial IVCFs or wires manipulate the filter during venous catheter exchanges (Fig. 53.8).

Diagnostic Evaluation of Inferior Vena Cava Filter Complications

Migration of IVCFs often is diagnosed intraoperatively or when a diagnostic imaging scan is performed for subsequent symptoms resulting from the migration. Thrombosis of the IVCF can also be diagnosed with a CT scan in the venous phase or venography. Late complications such as fracture, perforation or migration are usually detected by a CT performed for symptoms or unrelated problems (Fig. 53.9).

Management of Inferior Vena Cava Filter Complications

IVCF migration can be largely prevented with appropriate sizing and preoperative planning. When wire exchanges are necessary for line exchanges in the context of a patient with an IVCF, direct fluoroscopic wire exchanges limit manipulation

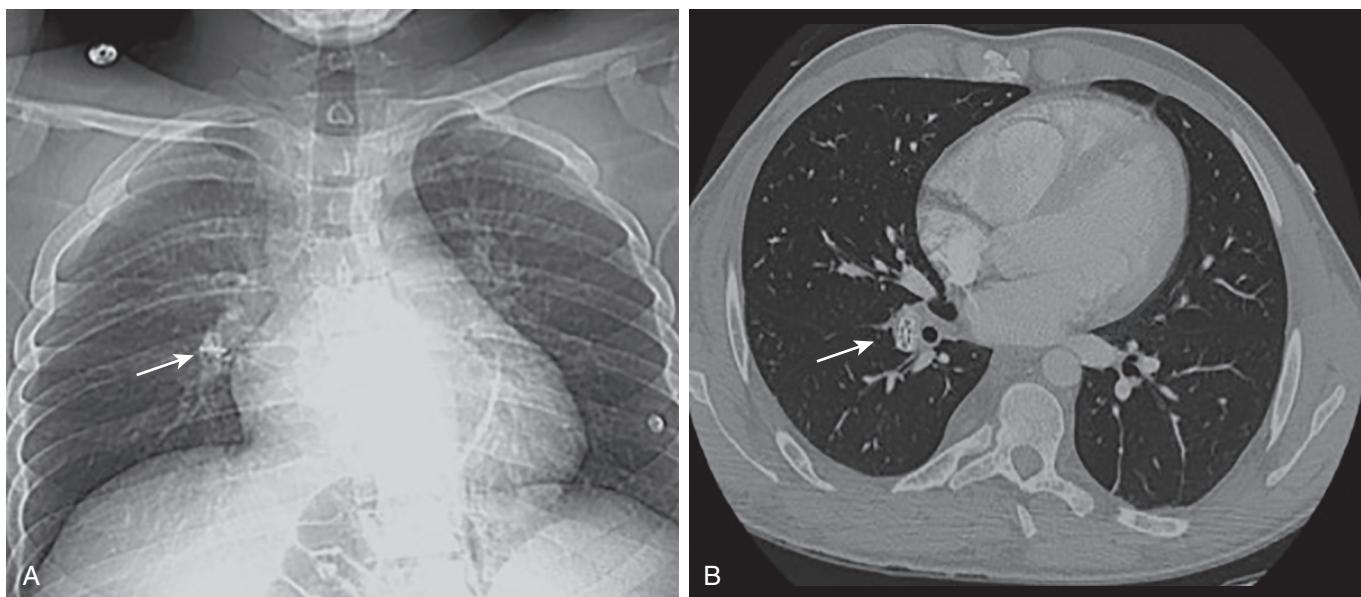


Figure 53.6 Embolization of an occlusion plug (arrows) from the right internal iliac vein into the pulmonary circulation, seen on chest X-ray (A) and CT scan (B).



Figure 53.7 Internal Iliac Vein Coiling in a Patient with Severe Pelvic Congestion. Sheath extends from the right iliac vein up and over to the left. Coils were anchored in the branches of the iliac vein (single arrow) and extended into the internal iliac (double arrow) for occlusion.

of the existing IVCF. Retrieval of a migrated IVCF usually involves percutaneous access of the internal jugular vein and femoral vein, while using large diameter sheaths to accommodate buddy wires, snares, and catheters. Filters may need to be crushed into large sheaths and extracted with a cutdown on the



Figure 53.8 Undersized inferior vena cava (IVC) filter placed near the hepatic veins in the IVC for caval thrombus extending above the renal veins.

femoral or internal jugular vein. If percutaneous methods fail, surgical exploration and extraction may be required, especially if lodged in the pulmonary artery and causing cardiac complications. There have been reports of robotic removal of IVCF in patients with complications, and this has the potential to decrease patient morbidity and recovery time when compared to open surgery.³⁷

Perforations of the IVCF legs are most often found incidentally on imaging studies. Most cases are asymptomatic, but

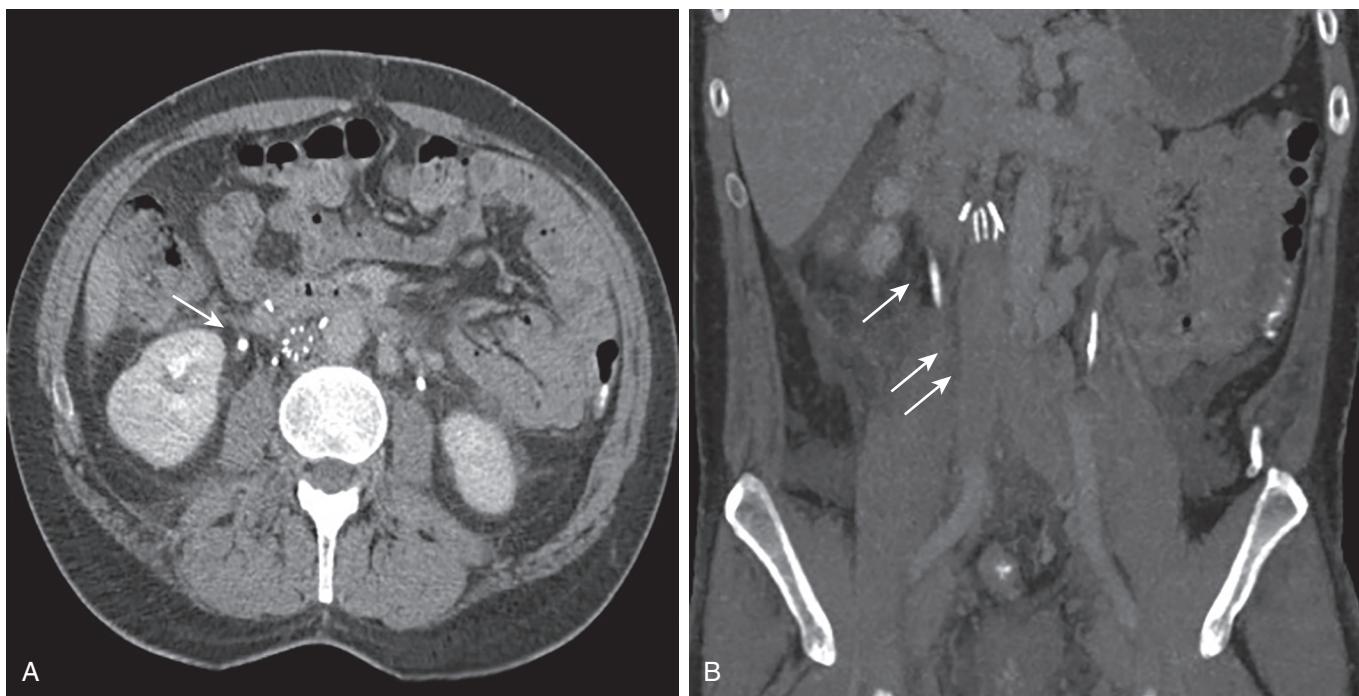


Figure 53.9 CT scan for abdomen and pelvis in sagittal (A) and reconstructed (B) views demonstrating strut fracture and migration (single arrow), thrombosis of inferior vena cava inferior to the filter (double arrows) and perforation of filter struts in the bowel retroperitoneum and near the aorta.

symptoms from penetration into adjacent structures such as the duodenum can occur. Treatment may require removal of the offending IVCF and open repair of the organ injury.

Thrombosed IVCF most often manifests with lower extremity swelling but can also be associated with chronic post-phlebitic syndrome, phlegmasia, and renal failure. Patency rates of IVCFs decrease with time; thus, filters should be removed as soon as clinically possible.³⁸ Patients with IVCF thrombosis (Fig. 53.10) can be considered for thrombolysis and removal of the IVCF, assuming no contraindications. In addition, patients with chronic caval obstruction may be considered for ilio caval venous reconstruction, especially to address lower extremity symptoms.³⁹

CONCLUSIONS

Venous complications typically arise because of trauma or iatrogenic injury. DVT is the most common venous complication and is treated with anticoagulation in most cases. Direct injury can be treated with repair or ligation, depending on the location. Late complications, such as AV fistula or migration of a venous device, are treated based on symptoms.

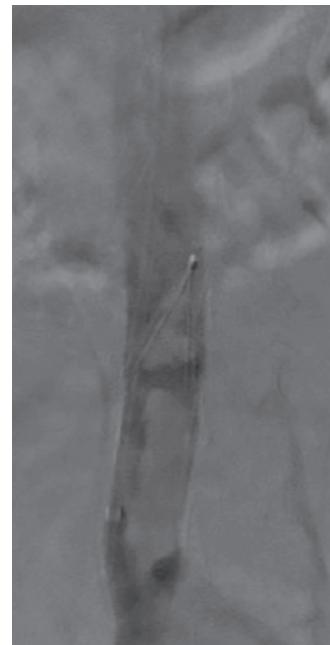
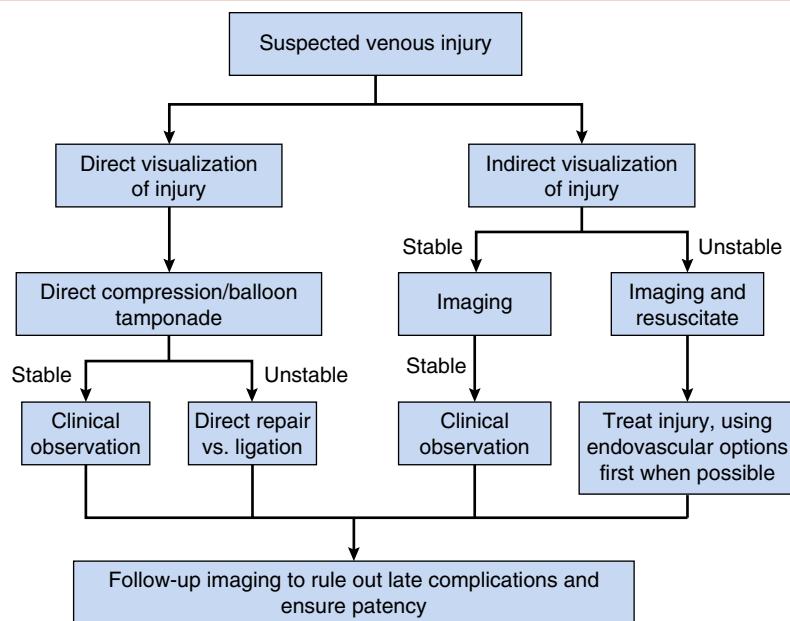


Figure 53.10 Inferior Vena Cava Thrombus at Time of Filter Retrieval.

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Local Complications: Lymphatic

AUDRA A. DUNCAN

INTRODUCTION	685	Diagnosis	689
POST-BYPASS EDEMA	685	Management	689
Etiology and Pathogenesis	685	CHYLOUS ASCITES	690
Diagnosis	686	Diagnosis	690
Management	686	Management	690
Prevention	686	Prevention	691
LYMPHATIC FISTULA	687	THORACIC DUCT FISTULA	691
Etiology	687	CHYLOTHORAX	691
Diagnosis	687	Diagnosis	691
Management	687	Management	692
GROIN LYMPHOCELE	688	Prevention	692
RETROPERITONEAL LYMPHOCELE	689	CHAPTER ALGORITHM	693

INTRODUCTION

Due to the close anatomic association between fine lymph vessels, lymph nodes, and corresponding arteries and veins, the possibility of lymphatic complications should always be considered when proceeding with vascular operations. Although the ability of transected or ligated lymphatics to regenerate and re-establish normal lymphatic transport is remarkable, extremity edema after vascular intervention is one of the most common complications. Injury to the lymphatics is a major contributor to the development of lower extremity edema after infrainguinal reconstruction,^{1–11} and can also occur after open venous surgery with groin dissection. Interruption of lymphatic vessels during surgical dissection may also cause a lymphatic fistula^{12–18} or lymphocele.^{17,19–28} Rarely, injury to the para-aortic or mesenteric lymphatics may result in chylous ascites.^{23,29–47} Thoracic duct injury may occur during cervical, thoracic, or thoracoabdominal aortic reconstruction,^{32,48–57} and chylothorax may occur after high translumbar aortography.⁵⁸

This chapter reviews the pathophysiology, diagnosis, and management of the most frequent lymphatic complications after vascular reconstruction and suggests guidelines for prevention.

POST-BYPASS EDEMA

Lower extremity edema occurs in 50% to 100% of patients who undergo open infrainguinal arterial reconstruction for chronic ischemia.^{2,7} Leg swelling after femoropopliteal or femorotibial bypass becomes evident with dependency, usually when the patient resumes ambulation. Pitting edema generally subsides within 2 to 3 months after reconstruction, although it may be persistent in some patients. Significant lymphedema can impair normal ambulation or delay wound healing despite successful arterial reconstruction.

Etiology and Pathogenesis

Lymphedema develops when the rate of production of protein-rich interstitial fluid exceeds the capacity of the lymphatic system to remove the increased lymph volume. When lymphatic transport fails, post-bypass edema occurs.⁵⁹ Lymphatic insufficiency has two main causes. First, increased production of interstitial fluid after successful revascularization results in a significant increase in the lymphatic load. Second, the transport capacity of the lymphatic system is reduced because of lymphatic injury and obstruction of deep and

superficial lymph channels during dissection in the groin and popliteal space and along the great saphenous vein.

Increased capillary filtration results from elevated arterial pressure after revascularization, alterations in the regulation of microcirculatory flow, and probable endothelial and smooth muscle injury from chronic ischemia.^{1,7} Eickhoff⁸ demonstrated that abnormalities in local blood flow regulation normalize approximately within a week after reconstruction, whereas edema persists much longer in these patients. Eickhoff's experiments support the theory that lymphatic obstruction secondary to surgical injury is the most important cause of post-bypass edema.

If the number of functioning major lymph channels decreases to a critical level, lymphedema develops. In patients studied with lymphangiography after infrainguinal bypass, the average number of patent superficial lymph vessels visualized was reduced to 1.7 per patient compared with the normal average of 9.5.¹ In a similar series of 37 patients, edema was not significant when more than three intact superficial lymph vessels were visualized on the postoperative lymphangiogram.⁴ AbuRahma et al.⁹ examined the involvement of the lymphatic system in the pathophysiology of edema formation in patients who underwent femoropopliteal bypass grafting. Edema developed in 29 of the 72 patients (40%). Leg swelling occurred in 85% (17 of 20) of the patients treated by conventional dissection of the femoropopliteal arteries. When careful dissection preserving lymphatics was performed, edema developed in only 2 of 20 patients (10%). Postoperative lymphangiography showed normal anatomy in six of the eight patients without edema, but markedly abnormal anatomy was in all eight patients with edema.

Persson et al.¹⁰ found less edema in patients who needed less dissection; that is, less edema in patients with prosthetic grafts compared to those with vein grafts and less edema in patients with above-knee grafts compared to below-knee bypasses.¹⁰ Studies using albumin clearance in patients with edema after revascularization also supported the idea that edema is mainly lymphatic in origin. A reduction in the plasma albumin level with a concomitant increase in albumin content in the extremity was noted after infrainguinal bypass.⁶⁰ The increase in albumin content was three times greater in limbs revascularized by femoropopliteal bypass than in those revascularized with aortoiliac grafts. These data correspond to the clinical observation that edema is less likely after aortofemoral revascularization.

Lymphedema with lymphocele has also been reported following varicose vein surgery. There is an association of lymphatic dysfunction in patients with incompetent varicose veins, and therefore one must take the same care to protect lymphatics during open vein surgery.^{18,61}

Although venous thrombosis has been proposed as a cause of postoperative leg edema,^{62,63} studies have demonstrated a low incidence of deep venous thrombosis in patients with post-bypass edema.^{64,65} In one series, normal venous hemodynamics and morphology were confirmed in 41 of 45 patients with leg edema after arterial bypass.⁶⁶ The incidence of deep venous thrombosis after femoropopliteal bypass was found to

be similar in patients who had edema (7%) and in those who did not (10%).⁹ Deep venous thrombosis therefore seems to play a minor role in post-bypass edema in most patients.^{7,59,67}

Diagnosis

Mild, partially pitting ankle edema appears on the second or third postoperative day and resolves almost completely with leg elevation and bed rest. Lymphedema is frequently unilateral and involves the dorsum of the foot ("buffalo hump") and the toes ("squaring"). The differential diagnosis of postoperative limb swelling includes deep venous thrombosis, infection with cellulitis, and compartment syndrome. The history and physical examination can aid in identifying cellulitis or compartment syndrome, and duplex scanning can diagnose deep venous thrombosis. If the cause of the edema is still in question, lymphoscintigraphy can confirm the presence of lymphedema (Fig. 54.1).

Management

Postoperatively, mild edema of the extremity should be treated by frequent elevation of the limb. Some surgeons advocate for strict bedrest. Cardiac failure should be treated promptly to help preserve the normal pressure gradient and allow venous return and lymph flow toward the heart. Moderate to severe post-bypass edema is treated with compression wrapping until the incisions have healed, followed by calf-length, 30- to 40-mm Hg compression stockings. For patients with a below-knee, *in situ* bypass or any bypass to the distal tibial or pedal arteries, management is individualized to avoid direct compression of a subcutaneous vein graft. Attempts to prevent or limit post-bypass edema pharmacologically with steroids, mannitol, terbutaline, or furosemide have not proved effective¹⁰ and are not recommended.

Prevention

Meticulous, lymph-preserving surgical dissection is needed to minimize post-bypass edema.^{9,59} For infrainguinal bypass, a vertical groin incision slightly lateral to the femoral pulse should be made in an attempt to preserve the patency and integrity of the lymph nodes.⁶⁸ The inguinal lymphatics should be retracted medially, and a vertical incision should be made in the femoral sheath to dissect the femoral arteries. Loupe magnification facilitates identification of the lymph nodes and lymph vessels. The lymphatics should be carefully preserved; if they must be divided, they should be ligated to avoid leakage of lymph. Attempts should be made to preserve as much lymphatic tissue as possible between the saphenofemoral junction and the femoral artery.

Multiple short skin incisions to harvest the saphenous vein may disrupt fewer superficial lymphatics.⁹ In theory, endoscopic video-assisted vein harvest may also cause less lymphatic injury and decrease wound-healing problems without compromising vein conduit quality. In a series of 68 lower extremity bypass procedures, only one bleeding complication was related



Figure 54.1 (A) Edema of the left lower extremity in an 88-year-old man 4 weeks after left femoropopliteal saphenous vein bypass performed for severe chronic ischemia. (B) Lymphoscintigraphy confirmed severe lymphedema of the left leg with no visualization of the lymph vessels or inguinal lymph nodes. Lymphatic transport was normal on the right.

to the video-assisted harvest, and two seromas developed at the arterial dissection sites.⁶⁹ The benefit of endoscopic versus open vein harvesting in terms of a reduced rate of lymphatic complications was confirmed in prospective randomized studies,^{70,71} and such harvesting can result in a reduction in postoperative wound infections.^{72,73} Dissection around the popliteal artery should be performed with the same care to avoid lymphatic disruption. The vascular sheath should be opened longitudinally without dissection of the popliteal vein or the posterior tibial nerve in the neurovascular bundle. Fibroadipose tissue, which contains the deep lymphatics in the popliteal fossa, should be left intact. Obara et al. reviewed 1580 open and endovascular surgery procedures and concluded that significant reductions in lymphatic complications occur with planned procedure, and endovascular procedures, as well as using minimal incision techniques for femoral artery exposures when possible.⁷⁴ More recently, Dessalvi et al. described the prophylactic use of lymphoscintigraphy and blue dye with or without lymphovenous anastomoses eliminated the risk of lymphatic complications associated with open venous surgery.¹⁸

LYMPHATIC FISTULA

Because of the rich lymphatic network in the femoral triangle, lymphatic fistulae after vascular reconstruction most often occur at the groin. In 4000 vascular operations, Kalman et al.¹⁶ observed lymphatic fistulae in 45 (0.1%) patients. The incidence of this complication was similar in other series and ranged from 0.8% to 6.4%.^{13,75,76}

Etiology

Important factors that contribute to lymphatic leakage are failure to ligate or cauterize divided lymphatics and failure to approximate the tissue layers properly at closure. Lymphatic

leakage occurs more frequently in older diabetic patients with poor wound healing. Excessive early limb motion, infection of the operated leg or foot, reoperation, and placement of a prosthetic graft to the groin are other possible causes.¹⁶

Diagnosis

Persistent leakage of clear or yellow fluid from a groin incision establishes the diagnosis. Lymphoscintigraphy to confirm that the fluid is of lymphatic origin is seldom necessary when the fistula develops within days or a few weeks after the operation. When lymphatic leakage occurs several months or years after vascular reconstruction, lymphoscintigraphy is helpful; in such cases, however, computed tomography (CT) white blood cell scanning, and sometimes fistulography, must be performed to exclude infection of an underlying vascular graft (see Ch. 49, Graft Infection). CT is also valuable for the diagnosis of concomitant retroperitoneal lymphatic injury, because a retroperitoneal lymphocele or chylous ascites can manifest as a lymphatic fistula at the groin.⁵⁹

Management

Early diagnosis and management of a lymphatic fistula are important to prevent prolonged hospitalization and delayed wound healing. Although infection of an underlying vascular graft may be rare, most studies have reported a small but definite risk of deep wound infection from persistent leakage of lymph.^{13,16} Conservative management is indicated in the first few days and should include local wound care, administration of systemic antibiotics, and bed rest with leg elevation to reduce lymph flow. Ideally, all lymphatic leakage will cease 7 to 12 days after initial drainage with conservative measures.⁷⁴

When the fistula continues to produce large volumes despite several days of conservative management, surgical closure

in the operating room is the best therapeutic option.^{13,16} Approximately 30 to 60 minutes preoperatively, 5 mL of isosulfan blue (Lymphazurin; United States Surgical, Norwalk, CT) dye is injected subcutaneously into the first and third interdigital spaces in the foot (Fig. 54.2).^{15,59} A sequential compression pump is placed on the affected leg to increase lymphatic and venous drainage. The groin incision is then opened, and the site of the lymphatic injury is apparent by the leakage of blue fluid (Fig. 54.3). The area is oversewn, and the wound is closed in multiple layers. If isosulfan blue is not visualized, the incision is irrigated and closed in layers with interrupted suture. When it is impossible to oversew the damaged tissue, injection of fibrin glue may also be useful.

Recently, the widespread use of vacuum-assisted closure (VAC) therapy has been suggested in the use of lymphocutaneous fistulae.⁷⁷ By placing VAC devices on 10 patients with either lymphocutaneous fistulae (4 patients) or lymphoceles (6 patients), which



Figure 54.2 Injection of isosulfan blue (Lymphazurin) dye into the first and third interdigital spaces of the foot immediately visualizes the foot lymphatics (arrow) and during surgery helps identify the site of lymphatic injury at the groin.



Figure 54.3 Intraoperative photograph of groin re-exploration demonstrating isosulfan blue (Lymphazurin) dye at the base of the incision (arrow). The dye allows localization of the lymphatic injury to facilitate ligation and fistula control.

converted to fistulae, the authors were able to treat all incisions without recurrence with a median outpatient VAC treatment duration of 16 days. Although this was an early study, it suggests that VAC therapy may be useful in recurrent lymphoceles or difficult-to-manage wounds.

GROIN LYMPHOCELE

A lymphocele is a localized collection of lymph. Early after injury to the lymphatic pathways, the lymph collects between tissue planes. Unless the lymph is reabsorbed spontaneously or drains through a cutaneous fistula, a pseudocapsule develops. In contrast to a seroma, a lymphocele usually has a well-localized connection with one or more of the lymphatic channels. For this reason, lymphoscintigraphy can readily demonstrate a lymphocele (Fig. 54.4). As with lymphatic fistulae, the most frequent site of lymphoceles after vascular reconstruction is the groin, often appearing within the first postoperative month. Large lymphoceles cause local discomfort, pain, and leg swelling. Hematoma, seroma, and wound infection should be considered in the differential diagnosis. The presence of a soft, fluid-filled cyst and intermittent drainage of clear lymph through a fistula confirm the diagnosis of lymphocele. Ultrasoundography is helpful in distinguishing a solid, dense hematoma from a cystic lymphocele. CT is performed when a lymphocele develops several weeks to months after the operation by excluding graft infection or identifying a retroperitoneal lymphocele extending to the groin.

Small lymphoceles can be observed because they may reabsorb spontaneously. For enlarging or symptomatic lymphoceles or lymphoceles that lie close to a prosthetic graft, early surgery to reduce the chance of graft infection should be performed. Injection of isosulfan blue into the foot is helpful for identifying the lymphatic channels supplying the lymphocele. The lymphocele is excised, and the lymphatic pedicle is ligated or oversewn (Fig. 54.5). The wound is closed in multiple layers over a small subcutaneous drain. Sclerotherapy, performed

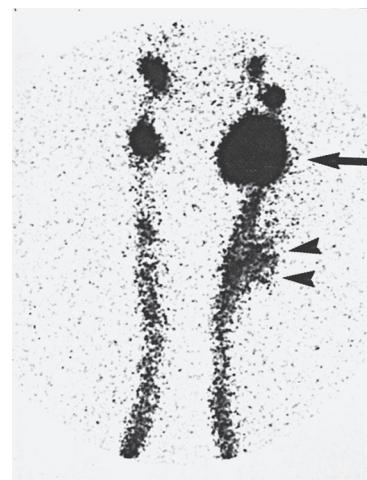


Figure 54.4 Bilateral lower extremity lymphoscintigraphy demonstrating a large left groin lymphocele (arrow) and extravasation of colloid in the left side of the thigh (arrowheads).

more frequently for retroperitoneal lymphoceles, can also be used for groin lymphoceles. Microsurgery with creation of lymphovenous anastomoses has been described to treat lymphedema, recurrent lymphocele and severe lymphorrhea in the groin, scrotum, and axilla.^{78,79}

Groin muscle flap coverage can be used to fill defects and provide a single-intervention management of lymphoceles. Shermak et al. reviewed the 22 muscle flaps (19 gracilis, 1 sartorius, 1 rectus abdominis, 1 rectus femoris) placed for lymphoceles. They found that biopsy specimens of the healed muscle at 1 year identified lymphatic channels, indicating that the muscle flap becomes a new path for lymphatic drainage.⁸⁰

RETROPERITONEAL LYMPHOCELE

Symptomatic retroperitoneal lymphoceles are rare. In a review of more than 4000 aortic reconstructions, an incidence of 0.1% was reported by Garrett et al.²⁶ In reviewing the literature,^{19,20,22–24,26,59} 11 well-documented cases of this complication were found after aortic reconstruction. The number of unreported and asymptomatic cases is undoubtedly higher. Retroperitoneal lymphoceles have been reported more frequently after renal transplantation (incidence of 0.6%–18%).^{27,81–83} In these patients, however, a lymphocele develops not only because of injury to the recipient pelvic lymphatics but also because of increased lymph production and leakage from the donor kidney.²⁷

Diagnosis

The most common symptoms of retroperitoneal lymphocele are abdominal distention, nausea, and abdominal pain, and the most frequent finding is an abdominal or flank mass. Although signs or symptoms may develop early, in almost half of patients, the lymphocele is discovered a year or several years after

the operation.⁵⁹ Patients with signs or symptoms of a retroperitoneal lymphocele should be examined with CT (Fig. 54.6). In 5 of 11 published cases of retroperitoneal lymphocele, a groin mass was also present.⁵⁹ Evaluation of these patients showed communication between the groin lymphocele and a retroperitoneal lymphocele. This observation illustrates the importance of CT when a groin mass develops after aortofemoral reconstruction. If infection is suspected, white blood cell scanning should also be performed, unless CT has already confirmed graft infection (see Ch. 49, Graft Infection). Lymphoscintigraphy can be diagnostic of a retroperitoneal lymphocele and should distinguish it from perigraft seroma. Nevertheless, lymphoscintigraphic confirmation of a lymphocele does not rule out graft infection.

Management

For patients with a small asymptomatic retroperitoneal lymphocele, observation with serial ultrasonography or CT is warranted. If the lymphocele enlarges or causes local compression of adjacent structures, needle aspiration under CT or ultrasound guidance is performed. This maneuver is both diagnostic and therapeutic. In 4 of 11 patients, aspiration alone was used with success.⁵⁹ Placement of an indwelling irrigation-drainage system is associated with a risk for infection. Garrett et al.²⁶ discussed two patients whose prosthetic grafts became infected after an irrigation-drainage system was placed for a retroperitoneal lymphocele. Therefore, when repeated aspiration is unsuccessful, sclerotherapy or operative repair should be considered. Abdominal exploration is performed after injection of 5 mL of isosulfan blue into the ipsilateral foot according to the technique detailed earlier. The lymphocele is unroofed, and the site of the lymphatic injury is oversewn, ligated, or both. If the prosthetic graft is exposed, it is covered by retroperitoneal tissue or omentum. When preoperative aspiration confirms the presence of chyle in the cyst, 24 oz of whipping cream is administered through a nasogastric tube 4 hours before exploration. Absorption of the cream helps identify the site of lymphatic leakage in the mesenteric lymphatics around the left renal vein or at the cisterna chyli (Fig. 54.7). Although

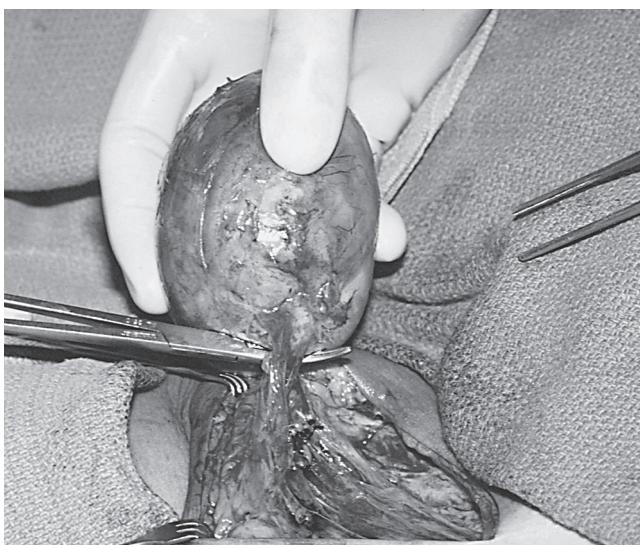


Figure 54.5 Intraoperative photograph of a dissected left groin lymphocele with an easily identifiable lymphatic pedicle. The pedicle was ligated, and the lymphocele was removed.

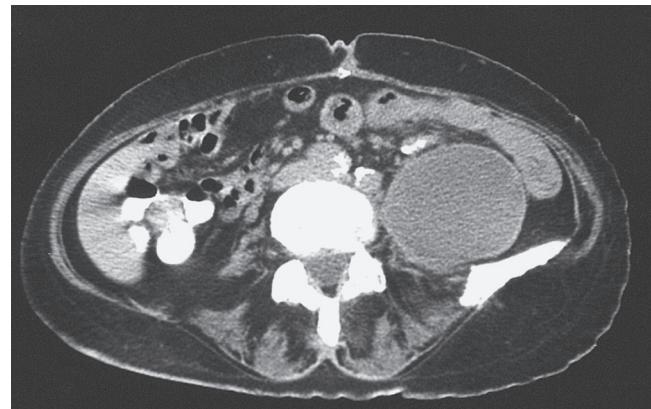


Figure 54.6 Computed tomography in a 70-year-old woman reveals a large left retroperitoneal lymphocele 9 months after repair of a thoracoabdominal aortic aneurysm.

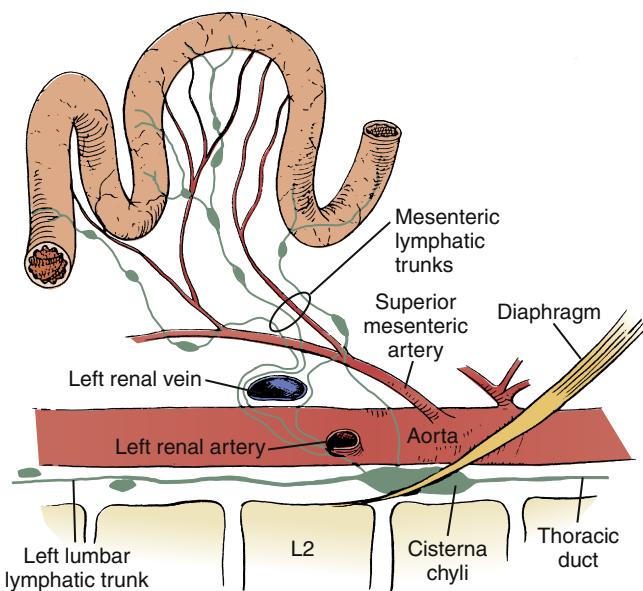


Figure 54.7 Anatomy of the mesenteric and ascending lumbar lymphatic trunks and the cisterna chyli. (Modified from Gloviczki P, Bergman RT. Lymphatic problems and revascularization edema. In: Bernhard VM, Towne JB, eds. Complications in Vascular Surgery. 2nd ed. St. Louis, MO: Quality Medical Publishing; 1991:366.)

the mesenteric lymphatic trunks should be ligated or oversewn, lateral closure of the cisterna may be attempted first with loupe magnification.

For post-transplant lymphocele, peritoneal fenestration has been recommended for treatment.^{81–83} Since the advent of surgical laparoscopy, however, several reports have described aspiration and peritoneal fenestration under laparoscopic visualization.^{82,83} A tongue of omentum is brought down and placed through the peritoneal window to prevent premature closure and recurrence of the cyst. One study analyzed the results of 12 laparoscopic and 23 open surgical internal marsupializations of pelvic lymphoceles. Laparoscopic lymphocelectomy required a longer operative time, but it resulted in a shorter hospital stay, faster convalescence, and fewer recurrences of the lymphocele.⁸¹ Laparoscopic transperitoneal drainage may become a useful addition to the vascular surgeon's armamentarium for the occasional treatment of lymphoceles after vascular reconstruction.

Percutaneous sclerotherapy has been used with increasing success as the definitive treatment of lymphoceles. Injection of talcum, bleomycin, doxycycline, povidone–iodine, fibrin sealant, and absolute alcohol has been reported, with good results in most cases.^{84–91} Treatment with repeated injections may be necessary.

CHYLOUS ASCITES

The development of chylous ascites after abdominal aortic reconstruction is rare, but the morbidity and mortality related to this complication can be significant. In a review of the literature, 23 patients were reported to have chylous ascites after aortic reconstruction.^{23,29–47,83} Eighteen patients (78%)



Figure 54.8 Computed tomography scan demonstrating diffuse ascites (arrows) in a patient 3 months after abdominal debranching and endovascular repair of a paravisceral aneurysm. Paracentesis confirmed the presence of chyle.

underwent repair of an abdominal aortic aneurysm, and five (22%) had surgery for occlusive disease. Ascites developed in the first 6 weeks after surgery in all but one patient.

Diagnosis

Symptoms of chylous ascites include progressive abdominal pain, dyspnea, and nausea. Abdominal distention can be significant, and the loss of proteins and fat may result in malnourishment. Lymphopenia and anemia can also develop and frequently result in poor immune function. Ascites can usually be detected by physical examination and confirmed by ultrasonography or CT (Fig. 54.8). Paracentesis is necessary to verify the presence of chyle in the ascitic fluid. Chyle is an odorless, sterile, alkaline fluid that is milky in appearance. Its specific gravity is higher than 1.012. Its protein content is usually more than 3 g/dL, and its fat content ranges from 0.4 to 4 g/dL. The fat in the fluid stains with Sudan stain.

Management

Although chylous ascites in patients with abdominal malignancies carries an ominous prognosis, the outcome when chylous ascites develops after open aortic surgery is somewhat better. Nevertheless, in one series, 4 of 23 patients with this complication after open aortic surgery died (mortality rate, 17%).^{23,32,48,92} The cause of death was sepsis in two patients, pulmonary embolism in one patient, and malnutrition in one patient.^{23,32,43,92} Most patients with chylous ascites after aortic surgery can be treated successfully without an operation.⁹³ The mainstay of treatment in patients with mild to moderate ascites is a medium-chain triglyceride diet to decrease chyle formation.⁹³ For severe cases, however, complete bowel rest and total parenteral nutrition must be instituted. Repeated paracentesis results in resolution of the symptoms in most patients. Placement of a peritoneovenous shunt has been reported, but may cause sepsis, leading to death.^{83,94} If repeated paracentesis is unsuccessful, exploration after ingestion of a fatty meal and closure of the site of the lymphatic injury should be performed.

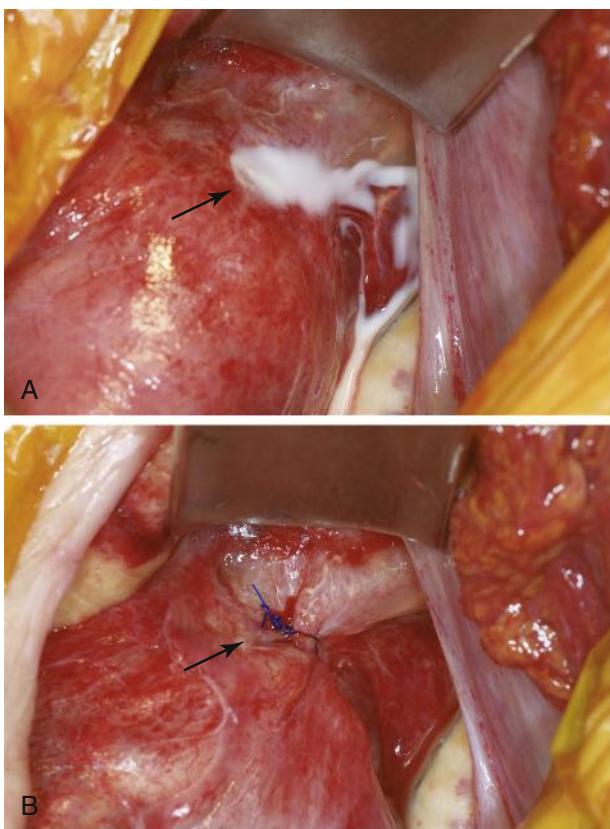


Figure 54.9 Intraoperative photographs of the patient described in Figure 54.8. (A) After ingestion of a fatty meal, chyle is easily visualized at the base of the mesentery (arrow) during abdominal re-exploration. (B) Successful ligation of the chylous injury and control of leakage (arrow).

(Fig. 54.9). Larger mesenteric or para-aortic lymphatic channels should be ligated or oversewn, but lateral closure of the injured cisterna chyli can be attempted with fine monofilament suture, as mentioned earlier. Of six reported patients who underwent exploration and surgical closure of the fistula, all recovered without recurrence.^{29,35,40,42,45,46}

Several case reports have described the use of laparoscopic techniques to control chylous ascites complicating nonvascular procedures.^{95–98} It is possible that these techniques may be used in patients with chylous ascites who do not respond to bowel rest and total parenteral nutrition after vascular procedures. In these cases, the patient first ingests a fatty meal. Laparoscopic lymphostasis is performed with a combination of laparoscopic clipping, electrocautery, and fibrin glue. Somatostatin and a low-fat diet may be used adjunctively in the postoperative period.^{95,98} Although these reports are preliminary, the concept of minimal-incision re-exploration is enticing, and early reports appear promising.

Prevention

Injury to the retroperitoneal and mesenteric lymphatics during aortic dissection should be carefully avoided. The cisterna chyli is formed by the right and left lumbar and the mesenteric lymphatic trunks; it is usually located at the level of the second lumbar vertebra, between the inferior vena

cava and the abdominal aorta.⁵⁹ In half of patients, a well-developed cisterna chyli is absent. Several large mesenteric lymph vessels are located on the anteroinferior aspect of the left renal vein (see Fig. 54.7). Injury to these vessels results in leakage of chyle. Failure to close the divided lymphatics may lead to the development of chylous ascites or retroperitoneal lymphocele. All large lumbar, para-aortic, and mesenteric lymph vessels should be ligated or clipped when division is necessary during aortic dissection. Lateral closure of the injured cisterna chyli should be attempted with 7-0 monofilament suture.

THORACIC DUCT FISTULA

Injury to the thoracic duct may occur after dissection of the proximal left common carotid artery or after left subclavian or vertebral artery dissection.²³ Neglected cases of thoracic duct cutaneous fistula may lead to malnutrition, lymphocytopenia, anemia, or infection of an underlying prosthetic graft. Early surgery plus lateral closure with 7-0 or 8-0 non-absorbable monofilament suture is the optimal treatment. If lateral closure is not possible, ligation of the thoracic duct at the neck is an accepted alternative because the collateral lymphatic circulation is usually adequate. The incision is closed over a subcutaneous drain, which is left in place for a short time postoperatively.

CHYLOTHORAX

Effusion of chyle into the pleural cavity after vascular procedures is uncommon; it occurs in just 0.2% to 1% of cases after cardiothoracic surgery.⁵⁶ It is more common in neonates and small children operated on for congenital vascular anomalies, most frequently for aortic coarctation.^{52–57} Chylothorax after repair of a thoracic aortic aneurysm has been reported,^{48–51} and in one patient it occurred after repair of an abdominal aortic aneurysm.³² Chylothorax may develop as a complication of transthoracic dorsal sympathectomy⁴⁹ or after high translumbar aortography.⁵⁸

Diagnosis

Pleural effusion is confirmed by chest X-ray studies or CT. Thoracentesis may reveal a milky fluid rich in albumin and lipids, although less than half will have a milky appearance.⁹⁹ Diagnostic criteria include a milky appearance, separation into a creamy layer on standing, absence of odor, specific gravity above 1.012, and triglyceride levels higher than 110 mg/dL (1.24 mmol/L).^{100,101} Analysis of the fluid obtained by thoracentesis or through the thoracostomy tube confirms the diagnosis. Laboratory analysis of the milky or serous fluid is similar to that described for chylous ascites. CT is performed to confirm effusion and exclude malignancy, although dilated lymphatics may also be seen on magnetic resonance imaging. Lymphoscintigraphy or lymphangiography is rarely required to identify the source of the chyle leak.¹⁰²

Management

Drainage of the chylous fluid through a thoracostomy tube is usually necessary to avoid respiratory compromise. The principles of treatment to decrease chyle formation are the same as those for chylous ascites. Conservative management consisting of closed drainage through a thoracostomy tube and nutritional support is effective in most cases. If a low-fat, high-protein diet with medium-chain triglyceride supplementation is not successful, intravenous hyperalimentation is started. Rarely, surgical closure of the site of leakage by oversewing or ligating the thoracic duct must be performed. Pleurodesis facilitates closure of the pleural space and decreases the potential for recurrence. Parietal pleurectomy is the most successful treatment when no distinct chylous leak can be identified.¹⁰⁰ Of six patients in whom chylothorax developed after aortic aneurysm repair, only one needed thoracotomy to treat a large chylous pseudocyst⁴⁸; however, one patient who was treated conservatively died after a long postoperative course that was complicated by both chylous ascites and chylothorax.³²

Cerfolio et al.¹⁰¹ at the Mayo Clinic reported 47 patients in whom chylothorax developed after thoracic operations. Nonoperative therapy was successful in a third, but 32 patients required ligation of the thoracic duct, and two were treated with mechanical pleurodesis and fibrin glue. Reoperation was successful in 31 of the 34 patients (91.2%). These authors recommended early reoperation and ligation of the thoracic duct when drainage was more than 1000 mL/day.

Multiple case reports have been published illustrating the role of thoracoscopic thoracic duct ligation in the treatment of chylothorax.^{103–111} Thoracoscopic clipping of the thoracic duct has replaced open thoracotomy in most patients.¹⁰² An early report from Cope and Kaiser¹⁰⁴ described percutaneous cannulation of the cisterna chyli and embolization of the thoracic duct with microcoils, particles, and glue. They reported on 42 patients who underwent percutaneous transabdominal catheter embolization or needle disruption of the retroperitoneum.¹⁰⁴ Cure or improvement was documented in 74% of the patients. Although rare, chylous ascites occurring after lymphatic puncture for thorax duct embolization for chylothorax has been reported.¹¹² In addition, a technique of direct lymphangiography using hybrid CT and fluoroscopy imaging that allowed direct placement of a 21-gauge needle into the cisterna chyli has been described.¹¹³

A summary paper from Kumar and Pawar in 2004 reported a total of 21 cases of video-assisted thoracoscopic surgery (VATS) for the treatment of chylothorax (16 patients), chylopericardium (four patients), and cervical chylous leak (one patient).¹⁰⁵ A trial of conservative therapy had failed in all patients, who then underwent clipping or ligation of the thoracic duct, except for one patient who had glue applied to the chylous leak site. All procedures were successful without complications. Ligation of the thoracic duct far above the diaphragm may be more successful than clipping of the cut near the diaphragm.¹⁰⁵ If extensive fibrosis is present, and

the thoracic duct is not easily identified, VATS may be used to ligate the mass of tissue between the azygos vein and the aorta.¹⁰⁵ One advantage of VATS for the treatment of chylothorax is that magnification of the thoracic structures can facilitate ligation. Because of the efficacy, low expense, and low morbidity of VATS for the management of chylothorax, early reoperation is recommended to avoid a lengthy conservative course with concomitant loss of chyle and a long hospital stay. Early intervention with VATS is recommended for patients with a high-output fistula (>1000 mL/24 hours), and a 1-week trial of conservative therapy is recommended in others.¹⁰⁵ However, if the chylous output remains greater than 200 mL/24 hours after 1 week, VATS intervention should be considered.¹⁰⁵

Prevention

Injury to the thoracic duct during thoracic aortic dissection should be carefully avoided. The thoracic duct extends upward from the cisterna chyli and enters the posterior mediastinum through the aortic hiatus, slightly to the right of the aorta and to the left of the azygos vein (Fig. 54.10). In the posterior mediastinum, it is mostly a right-sided structure. The thoracic duct enters the superior mediastinum behind the aortic arch and subclavian artery, to the left of the esophagus. It is thus exposed to injury during dissection of the proximal thoracic aorta, the aortic arch, or the proximal subclavian artery. Once injury to the thoracic duct is recognized, an attempt at ligation or closure should be made with loupe magnification. If it is not successful, ligation of the thoracic duct should be performed. Adequate collateral lymphatic circulation usually develops.

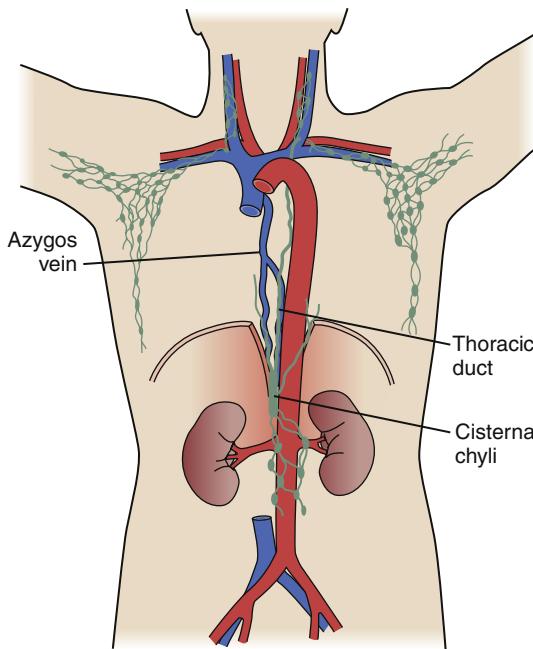
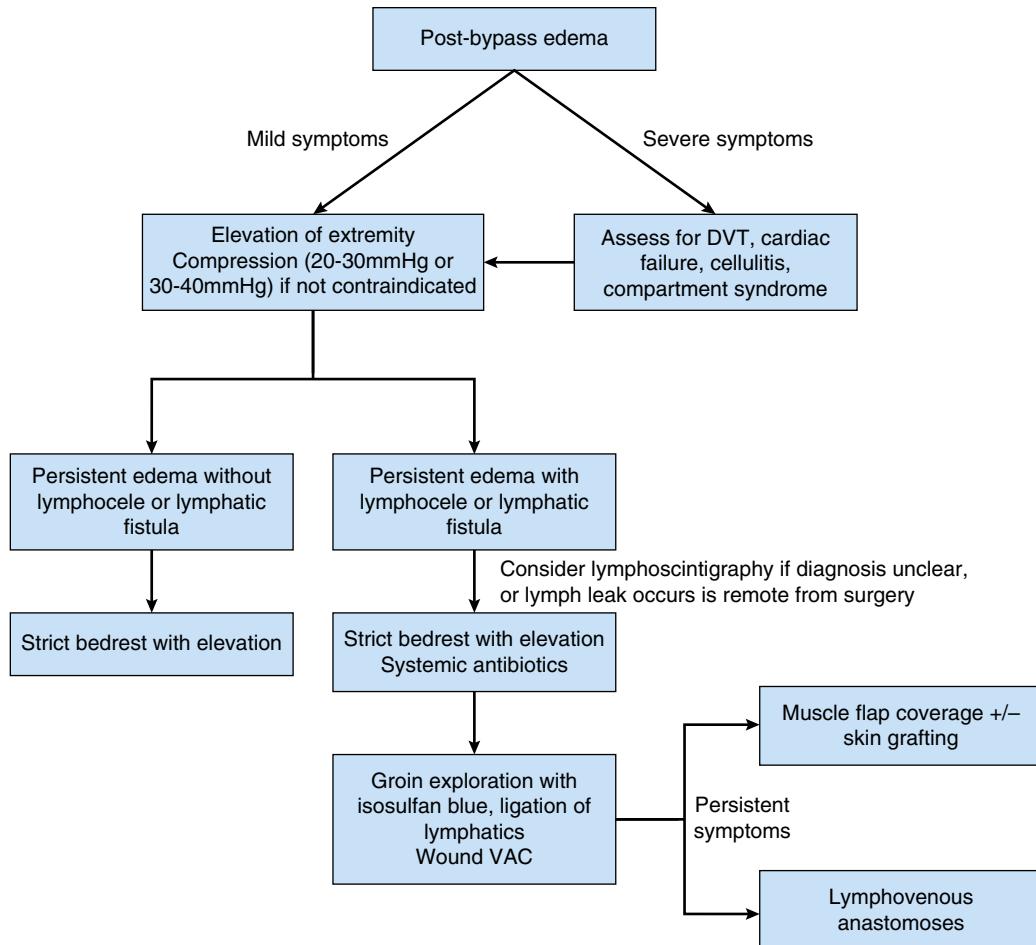


Figure 54.10 Anatomy of the thoracic duct. (By permission of the Mayo Foundation.)

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Thoracic and Thoracoabdominal Vascular Exposure

RHUSHEET PATEL and WILLIAM J. QUIÑONES-BALDRICH

INTRODUCTION 694

EXPOSURE OF THE ASCENDING AORTA AND AORTIC ARCH 694

Median Sternotomy 694

Position 695

Incision 695

Dissection 695

Mini-Sternotomy 695

Position 696

Incision 696

Dissection 696

EXPOSURE OF THE DISTAL AORTIC ARCH AND DESCENDING THORACIC AORTA 696

Trans-Sternal Bilateral Thoracotomy (Clamshell) 696

Position 696

Incision 696

Dissection 696

Left Posterolateral Thoracotomy 696

Position 696

Incision 696

Dissection 697

EXPOSURE OF THE DESCENDING THORACIC AORTA AND PARAVISCERAL AORTA 697

Position 697

Incision 697

Thoracic Dissection 697

Abdominal Dissection (Retroperitoneal) 698

EXPOSURE OF THE ABDOMINAL AORTA 698

Retroperitoneal Approach 698

Position 700

Incision 700

Dissection 701

Transperitoneal Approach 702

Position 702

Incision 702

Dissection 702

INTRODUCTION

Surgical exposure of the aorta involves three main segments: the ascending aorta and aortic arch, the descending thoracic aorta, and the abdominal aorta. Depending on the pathology, either one or several of these segments will need exposure simultaneously. This chapter presents the various incisions, techniques, and key elements for exposure of each aortic segment or combinations of segments.

EXPOSURE OF THE ASCENDING AORTA AND AORTIC ARCH

Median Sternotomy

The median sternotomy exposure is an optimal method to access the chambers of the heart, the ascending aorta, and the majority of the aortic arch. As a result, it is the most common exposure technique for operations involving the ascending aorta and/or the great vessels.

Position

The patient is placed supine on the operating room table, with arms tucked along the patient's side to relax the musculature and allow opening of the mediastinum and chest space.

Incision

An incision is made from just below the suprasternal notch to the tip of the xyphoid process. This incision can be extended for additional exposure of the aortic arch vessels, either along the anterior borders of the sternocleidomastoid muscle for exposure of the left or right common carotid arteries or superiorly along the midline for greater overall exposure. The latter should be avoided for cosmetic reasons. If additional exposure of the right subclavian artery is required, the incision can be carried along the superior border of the clavicle. Although an anterior 3rd or 4th intercostal space thoracotomy is the approach typically used for exposing the left subclavian artery, the very proximal part of the left subclavian artery can also be reached through a median sternotomy. Extension into a left supraclavicular incision may be needed for further distal control. An additional anterior 3rd or 4th intercostal space thoracotomy with creation of a trap door thoracotomy can be added to obtain exposure of the full continuum of the left subclavian artery in extremis patients with challenging traumatic injuries.

Dissection

Electrocautery is used to divide the subcutaneous tissue down to the pectoral fascia, which is also divided. The periosteum is then scored along the midline an equal distance from both sides of the intercostal spaces. The interclavicular ligament at the top of the sternal notch is divided. The tissues on one side of the xyphoid process are released, though some surgeons prefer to resect the entire process. The sternum is divided along the midline using a sternal saw, taking care to hug the back of the sternum with the toe of the saw. It is imperative to hold

mechanical ventilation at this time to avoid inadvertent pleural tears. Electrocautery is then used to achieve hemostasis along the anterior and posterior edges of the sternum. Manual pressure and a small amount of bone wax can be used to achieve hemostasis of the bone marrow. Once the sternopericardial ligaments are divided and the pericardium is freed from the posterior sternum, the sternal retractor is placed and progressively opened to achieve homogeneous retraction. Excessive retraction should be avoided to prevent sternum and/or rib fracture with potential dislocation of costochondral junctions. The vessels arising from the internal thoracic artery and draining into the brachiocephalic vein are identified and ligated. This allows full mobilization of the brachiocephalic vein. The anterior pericardium is then opened vertically to access the ascending aorta and origin of the aortic arch vessels (Fig. 55.1A). In certain circumstances, it may be necessary to ligate the left innominate vein, which is often well tolerated. Following these maneuvers, the ascending aorta, the aortic arch, and the innominate and left common carotid arteries can easily be identified and dissected free from surrounding tissues. The right vagus and right recurrent laryngeal nerves must be avoided during dissection of the distal portion of the innominate artery. It should be recognized that the vagus nerve courses anterior to the subclavian artery at its origin, with the recurrent laryngeal nerve originating from the vagus nerve and coursing posterior to the subclavian artery origin, creating a sling where the subclavian artery rests. Exposure of the innominate artery bifurcation can be obtained, often requiring caudal retraction of the left innominate vein.

Mini-Sternotomy

The mini-sternotomy was first described in 1949 by Holman and Willett.¹ Today, it is commonly used as an alternative to the median sternotomy for valve replacements, aortic root replacements, and ascending aortic aneurysm repairs. Its benefits

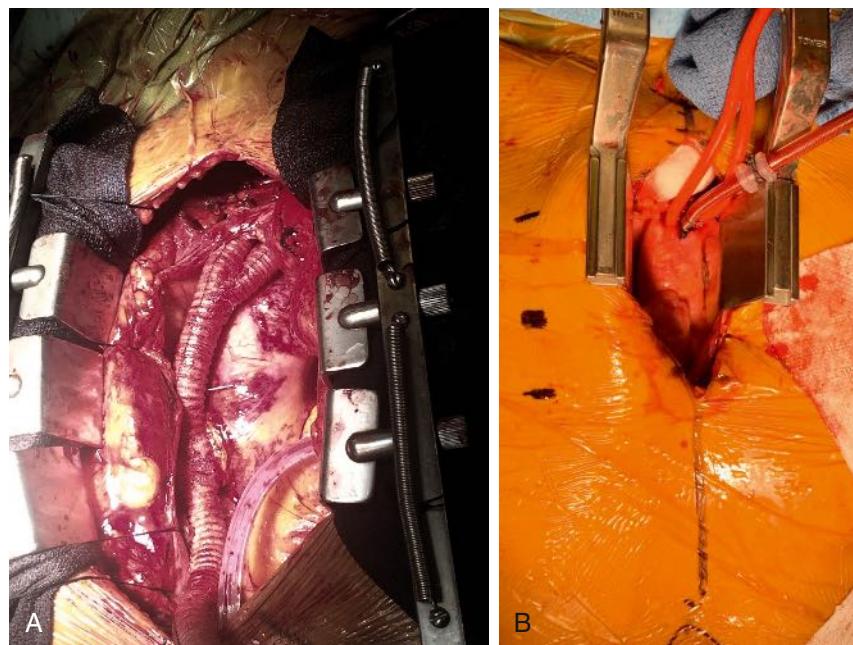


Figure 55.1 (A) Exposure of the ascending aorta. The median sternotomy allows ample exposure of the ascending aorta and the proximal branches. This image shows an aorto-innominate graft with second limb traveling to the left carotid artery. A third limb traveling caudally will be used as a conduit to place an endograft. The two cranial limbs travel posterior to the brachiocephalic vein. (B) Mini-sternotomy exposure.

include reduced trauma and a lower risk of sternal instability. It is also commonly used in re-operative cardiac surgery to reduce the risk of ventricular injury during sternal retraction. The advantages of this technique include decreased post-operative pain, decreased blood loss, and decreased adhesions around the right ventricle, as this region is not dissected during this exposure.² A number of studies by Svensson and colleagues have expounded on the benefits of minimally invasive sternotomy techniques. In one report of 54 patients undergoing mini-sternotomy for ascending aortic and arch repairs, the mortality and incidence of stroke were 4% and 3.7%, respectively, indicating that this method was safe for use in ascending and aortic arch repairs. Eighteen of these patients were redo sternotomies.³ However, this approach may not be suited for those with chest wall abnormalities such as pectus excavatum or morbidly obese patients.

Position

As with a full sternotomy, the patient is placed supine on the operating room table, with arms tucked along the patient's side.

Incision

There are various approaches to division of the sternum, including the upper reversed "T" and upper "J" or "L" incisions, which are the most commonly employed incisions to expose the superior mediastinum. Both incisions often provide adequate exposure to the aortic arch and the proximal portions of the innominate artery and vein. Moreover, conversion to a full median sternotomy is always an option when exposure is inadequate using this technique. An upper reversed "T" approach begins at the sternal notch caudally, before transecting the sternum at the level of the 3rd or 4th intercostal space (Fig. 55.1B). The "J" approach begins at the sternal notch and comes across the right 3rd or 4th intercostal space. Transesophageal echocardiography may be used to aid in determining the caudal extent of the incision.²

Dissection

The sternum is divided in the midline and then transversely, taking care to avoid injuring the internal mammary arteries, which lie just lateral to the sternum. For additional exposure the internal mammary arteries are ligated. A self-retaining retractor is then placed to separate the upper portion of the sternum and the dissection is continued in the same fashion as a full sternotomy.

EXPOSURE OF THE DISTAL AORTIC ARCH AND DESCENDING THORACIC AORTA

Trans-Sternal Bilateral Thoracotomy (Clamshell)

The trans-sternal bilateral thoracotomy incision is used in traumatic situations, lung transplantation, single-stage operations,

as well as for repair of aortic arch and proximal descending aortic pathology. This technique is most useful for exposures that require not only arch access, but also access to the descending aorta. As with the mini-sternotomy, the clamshell incision may be used in redo operations. The major disadvantage of this exposure is the need for prolonged ventilatory support postoperatively as compared to a median sternotomy. Postoperative pain is also increased with this approach.

Position

The patient lies in the supine position with the right arm alongside the chest. The left shoulder and hip are slightly raised with bumps.

Incision

An incision is made from the mid-clavicular line on the right to the anterior axillary line on the left at the level of the 4th intercostal space.⁴

Dissection

Dissection is carried down through the intercostal muscles in the fourth intercostal space, and both internal mammary arteries are ligated and then divided. The sternum is then divided transversely using a saw in the transverse plane. Using rib spreaders, the thoracic cavity is exposed. The pericardium and pleural reflections are dissected free from the posterior portion of the sternum. The left lung is mobilized and retracted away from the region of interest.

Left Posterolateral Thoracotomy

Exposure of both the distal aortic arch and proximal descending thoracic aorta may be accomplished using a left posterolateral thoracotomy. This exposure requires tolerance for single lung ventilation.

Position

The patient is positioned in the right lateral decubitus position with the left arm placed above the head on a padded armrest. The table break should be in line with the top of the patient's pelvis. The right arm is extended at 90 degrees to the operating room table with the elbow partially flexed to avoid traction of the brachial plexus. Padding is placed between the legs with the right leg flexed at the knee and the left leg extended resting on top of the padding. An axillary roll is placed under the right shoulder to support the shoulder girdle. The bed can be hyperextended to increase the space between ribs.

Incision

A curvilinear incision is started at a point midway between the medial border of the scapula and the thoracic spine along the 4th intercostal space along the inframammary crease. This can be extended medially for additional exposure of the aortic arch vessels. In cases involving the aortic root, the sternum can be transected but this requires sacrifice of the internal mammary artery.

Dissection

Following skin incision, flaps are raised and the anterior edge of the latissimus dorsi incised vertically. The plane between the latissimus and the serratus anterior is developed. Following this, the posterolateral edge of the serratus muscle is incised and the muscle is elevated. The latissimus dorsi is retracted posteriorly, and the serratus retracted anteriorly, thereby exposing the intercostal space. The 4th intercostal space is identified and entered on the superior portion of the rib to avoid injury to the neurovascular bundle. The pleural sac is appreciated and opened with a fine-tipped scissors. A ratcheted, self-retaining chest wall retractor, such as a Finochietto retractor, is then carefully placed between the ribs at the incision site and slowly opened. Intrathoracic extension of the intercostal muscle division is helpful in achieving maximal exposure while avoiding rib fractures. If the distal portion of the descending aorta is involved in the operation, the fifth rib may be resected for adequate exposure. The left lung is deflated and retracted to expose the descending aorta. The vagus, recurrent laryngeal, and phrenic nerves are identified and protected just proximal to the origin of the left subclavian artery. The aorta is then mobilized and intercostal arteries are ligated. In patients with thoracoabdominal aneurysms, the incision can be extended through the retroperitoneum, dividing the costochondral margin as is described below.

EXPOSURE OF THE DESCENDING THORACIC AORTA AND PARAVISCERAL AORTA

This approach will allow for exposure of the thoracic and abdominal aorta. The incision and dissection will vary depending on the level of exposure required. Due to the location of the aorta, this incision crosses both the thoracic and abdominal cavity, making it difficult to stay within anatomic boundaries. When possible more limited incisions should be utilized; it is important to note that the abdominal part of the aorta can be reached through an extraperitoneal (retroperitoneal) or transperitoneal approach. In the extraperitoneal approach, the aorta is exposed through the retroperitoneum without entering the peritoneal cavity, avoiding bowel manipulation and limiting fluid loss. In the transperitoneal approach, the peritoneal cavity is entered and the aorta and its branches are exposed using a left medial visceral rotation. The latter is typically used when access to the distal visceral vessels and/or right renal artery is necessary. The right common iliac bifurcation can be reached with either approach.

Position

The patient is placed in modified right lateral decubitus position with the shoulders at 60 degrees to the table (Fig. 55.2). The hips are rotated up to 45 degrees and partially flexed with the legs parallel to the bed. This allows access to both groins. The left arm is placed in a sling above the patient's head to enable proper rotation of the upper body, and a shoulder roll is placed under the chest to ensure the right shoulder is free from pressure. The operating table is



Figure 55.2 Positioning for exposure of the thoracoabdominal aorta. The body is placed in a lateral decubitus position with the operating table extended to provide maximum exposure.

hyperextended to open the space between iliac crest and costal margin. Once the patient is in the appropriate position, a moldable beanbag that was previously placed to sit between the patient and the operative table is secured by vacuum suction.

Incision

Prepping and draping should allow for access to the left thorax and the abdomen caudally for exposure of the distal aorta and right common iliac artery. A gentle curve near the superior portion of the incision reduces the risk of tissue necrosis at the apex of the lower portion of the musculoskeletal tissue flap as the incision crosses the costal margin. The more superior the exposure of the aorta, the more medial and superior the incision travels, with the incision traversing the skin from the tip of the scapula, along the 5th, 6th, or 7th intercostal space, according to the desired level of exposure (Figs. 55.3 and 55.4). To expose portions of the distal aortic arch, it may be necessary to enter the space between the 3rd and 4th rib through the same skin incision but as a separate thoracotomy incision (double thoracotomy).

Thoracic Dissection

To expose the thoracic aorta, the latissimus dorsi, anterior serratus, and rectus muscles are divided by electrocautery. The pleural space is entered after single right-lung ventilation is initiated. The subcostal margin is cut with either electrocautery or scissors at the lower intercostal space and the incision is linked downward with the abdominal portion of the incision. The entire rib or the anterior section of the rib of the particular interspace can be resected to aid in exposure. Once the pleural space is entered, the inferior pulmonary ligament is divided with cautery, ligating any vessels within it.

A self-retaining retractor is anchored on the left of the bed and the lung can then be gently retracted superiorly and laterally to expose the distal portion of the thoracic aorta. Pulmonary manipulation should be kept to a minimum. The proximal descending aorta can be separated from the surrounding mediastinal tissue to expose the origin of the left subclavian artery. The vagus nerve and recurrent laryngeal nerve are in



Figure 55.3 Incision used to repair a type III thoracoabdominal aortic aneurysm. Exposure of both the abdominal and thoracic aorta requires an incision that crosses anatomic boundaries.

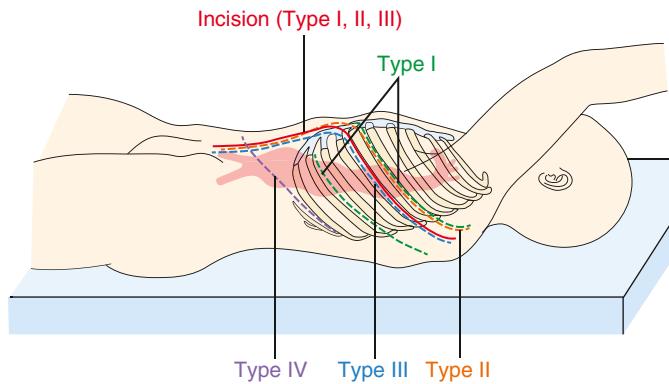


Figure 55.4 Skin incisions and superficial dissection for thoracoabdominal aortic (TAA) exposure. The red line indicates the skin incision for exposure of Type I to III TAA aneurysms. Manipulation of this skin incision allows for multiple entry points into the thoracic and abdominal cavities based on aneurysm location. The plane used for superficial dissection, including the appropriate rib space to enter the pleural cavity, is shown with the various green, gray, and orange dotted lines for TAA aneurysms I to III. The blue dotted line indicates both the skin incision and the superficial dissection plane for type IV TAA aneurysms.

close proximity to the aorta, just proximal to the subclavian artery, and care should be taken not to injure these structures during this portion of the dissection. The thoracic aorta is then circumferentially dissected and thus separated from the esophagus, which lies just anterior and medial to the aorta. The diaphragm is radially divided to avoid injury to the phrenic nerve for several centimeters near its peripheral attachment to the posterolateral chest wall for maximal exposure. Some surgeons advocate partial division of the diaphragm in an attempt to decrease postoperative pulmonary complications. This decision is often dictated by the anatomy and complexity of the exposure. Often, severe tortuosity, particularly when the descending aorta is to the right of the midline, requires more extensive division of the diaphragm.

Abdominal Dissection (Retroperitoneal)

Abdominal aortic dissection is initiated by dissecting down to the abdominal wall fascia lateral to the rectus abdominis muscle. The anterior sheath is divided longitudinally. Medially, the rectus muscle and associated fascia can be divided if additional exposure is required. It is often better to mobilize the rectus from medial to lateral to avoid denervation. Craniocaudally, the dissection is continued by dividing the external oblique, internal oblique, and transversalis muscles to identify the peritoneum (Fig. 55.5). The transversalis fascia is also divided longitudinally, allowing for a two-layer closure at the end of the procedure. Great care must be taken not to disrupt the peritoneal lining, as it is thin and often difficult to distinguish from the transversalis fascia. Difficulty in separating the “peritoneum” from the abdominal wall is often due to incomplete division of the transversalis fascia. Once the peritoneum is identified, it is separated from the abdominal wall using a combination of manual dissection and gentle traction.

The peritoneum and the abdominal viscera are retracted to the right to reveal the retroperitoneal fat. The plane between the retroperitoneal fat and the psoas muscle is then created and traced superiorly to the diaphragm. Gerota's fascia and the contained left kidney are included with the peritoneal contents and lifted anteromedially to expose the infrarenal and visceral segments of the aorta. The parietal peritoneum is dissected free from the peri-aortic fat and rolled medial to expose the anterior portion of the aorta and identify the proximal portions of the visceral vessels. The right renal artery will not be visible with this exposure unless the infrarenal aorta is either transected or fully mobilized. The left ureter will be on the back of the peritoneal sac and should be identified as it crosses the iliac artery (Fig. 55.6).

The left renal artery is identified to orient the visceral aortic dissection (Fig. 55.7). A relatively constant structure nearby the left renal artery origin is the reno-lumbar vein, which rises from the psoas groove to enter the renal vein, taking a course around the left side of the aorta. This vessel must be identified and ligated to allow the kidney to be retracted further medially. In rare circumstances, a retro-aortic left renal vein prevents this retraction. In that situation, the kidney can be left in its native position (see below) with the renal vein ligated distal to the adrenal and gonadal vein to allow collateral drainage. Ligation with planning of re-anastomosis is extremely difficult due to retraction, which creates tension during repair and should be avoided.

The diaphragmatic crus is divided, freeing the visceral aorta and allowing greater mobility of the aorta during the operation (Fig. 55.8). Further mobilization is aided by dividing the median arcuate ligament. With these maneuvers, the origins of the left renal artery, the superior mesenteric artery, and the celiac artery can all be identified and circumferentially dissected and controlled (Figs. 55.9 and 55.10).

EXPOSURE OF THE ABDOMINAL AORTA

Retroperitoneal Approach

The retroperitoneal approach is used to expose the distal descending and abdominal portion of the aorta including the paravisceral segment. This allows for excellent exposure of the

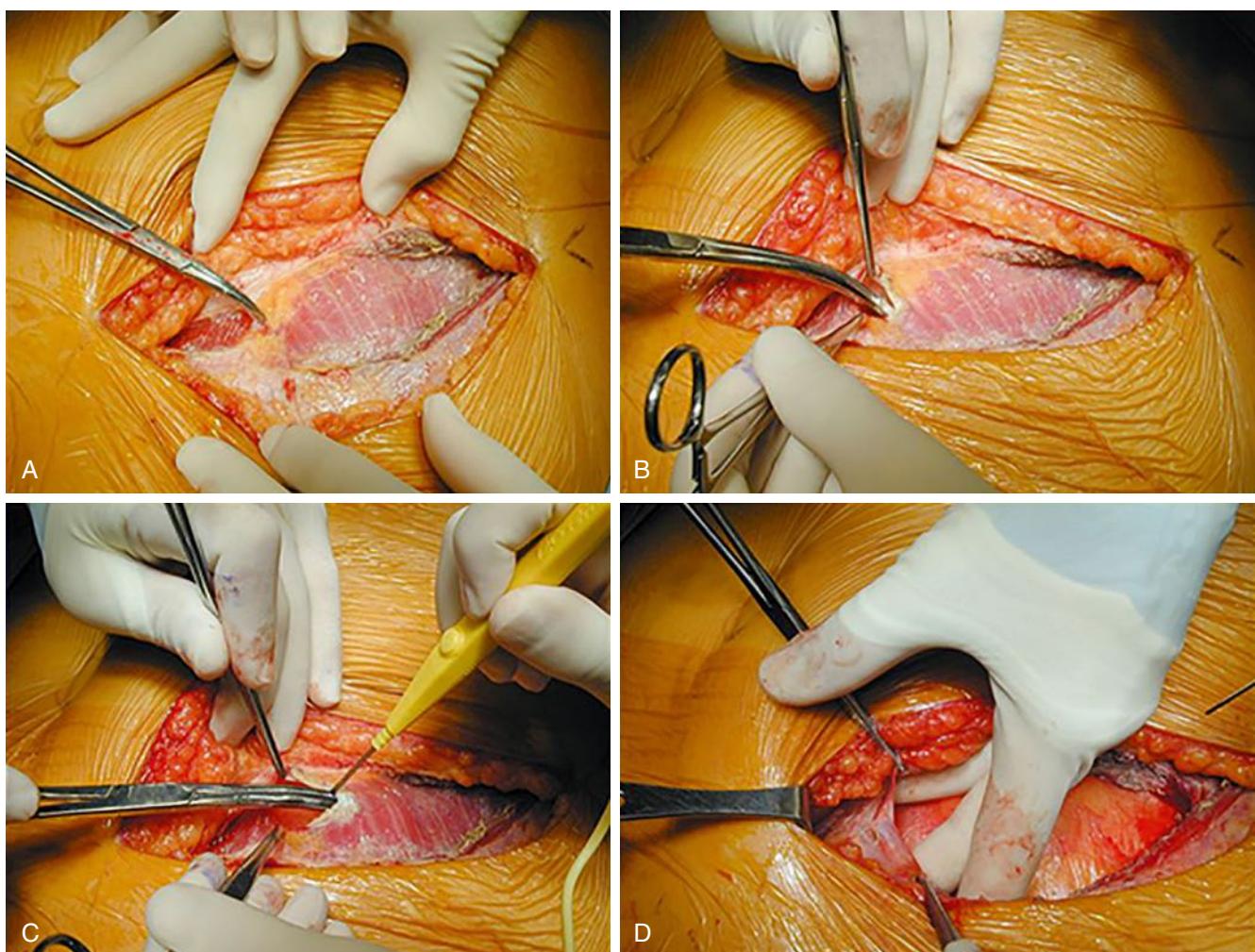


Figure 55.5 Layers of the Abdominal Wall. This panel shows the identification of the lateral border of the rectus muscle (A), followed by the dissection of the external oblique, internal oblique, and transversus abdominis musculature (B,C). Ultimately, the peritoneal lining is identified (D).

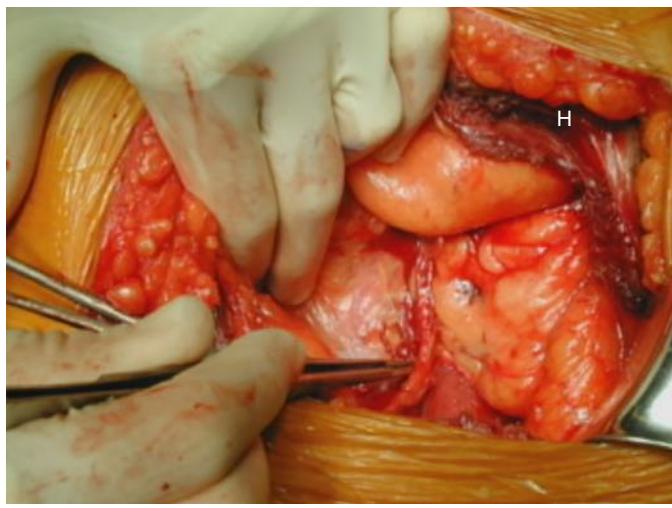


Figure 55.6 Ureter lying within the retroperitoneal fat. In this image, it is identified and reflected posteriorly to allow the left kidney to remain in its anatomic position.

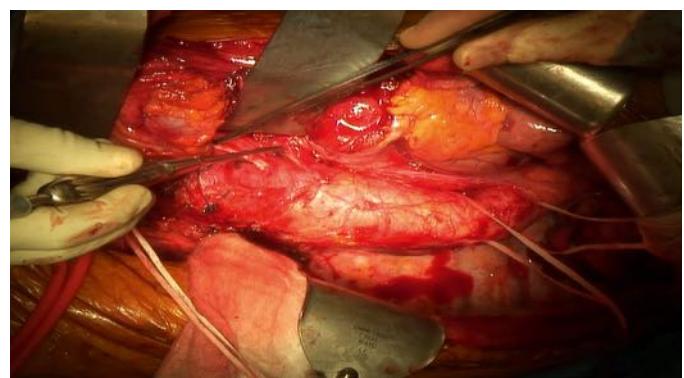


Figure 55.7 Exposure of the Thoracoabdominal Aorta. The left renal artery is identified at the tip of the surgeon's forceps as it courses posterior to a metal suction device. Identification of the left renal artery helps orient the surgeon to the remaining visceral vessels.

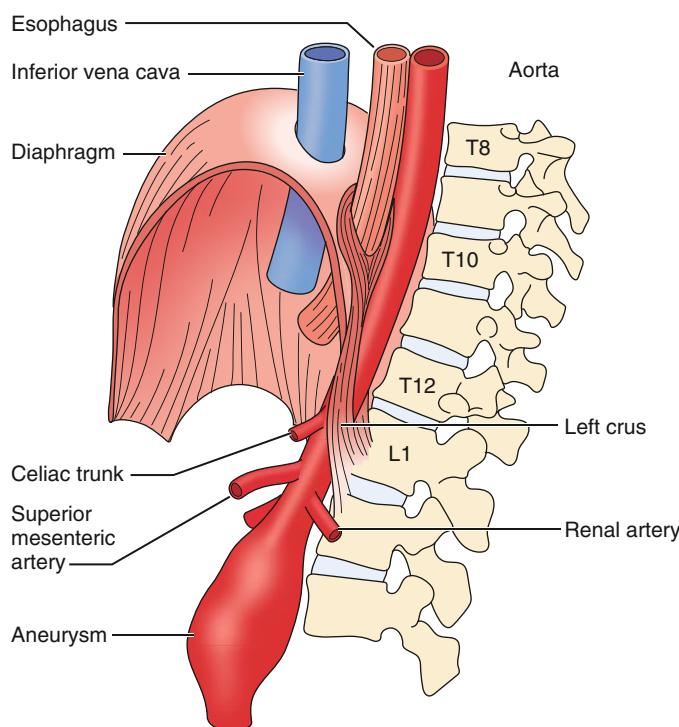


Figure 55.8 Sagittal view of the aorta and adjacent structures. The left crus of the diaphragm overlies the aorta proximal to the renal artery at the same level as the first lumbar vertebrae. Division of this structure allows access to the paravisceral aorta and descending aorta from within the abdominal cavity.



Figure 55.9 Exposure of the visceral aorta after dividing the diaphragmatic crus. A Rommel tourniquet is around the descending thoracic aorta.

proximal abdominal aorta while not violating the peritoneal cavity, making it ideal for treating paravisceral aortic pathology and type IV thoracoabdominal aneurysms (see Ch. 56, Abdominal Vascular Exposures).

Several studies have demonstrated reduced time in the intensive care unit and reduced time until return of bowel function using a retroperitoneal approach compared to a transperitoneal approach.^{5,6}

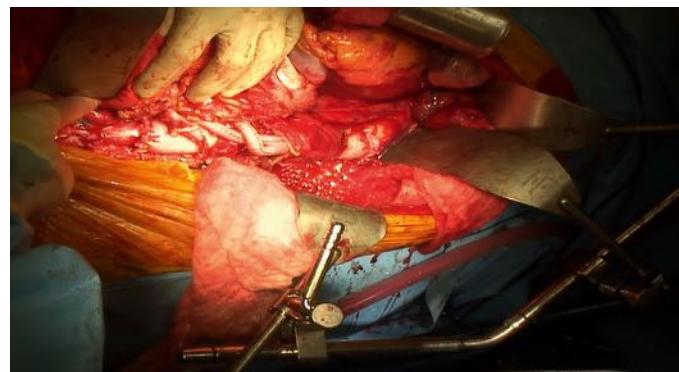


Figure 55.10 Complete replacement of the thoracoabdominal aorta. Note the three smaller caliber grafts anastomose with the left renal, superior mesenteric, and celiac arteries.



Figure 55.11 Incision used for a retroperitoneal exposure of the aorta. Note the groin incisions used to expose the femoral arteries. When positioning a patient for a retroperitoneal exposure, both groins should be accessible.

Position

The patient is placed in modified right lateral decubitus position similar to the positioning for a thoracoabdominal exposure. However, in this case, the hips are rotated only 20 to 30 degrees and the right leg is partially flexed.

Incision

A curvilinear incision begins in the midline between the umbilicus and pubic symphysis and is carried laterally to the 10th or 11th intercostal space (Fig. 55.11). For exposure that focuses on the cranial portion of the abdominal aorta, the incision can be further extended along the intercostal space, recognizing that the more cranial the incision, the more likely the pleural cavity will be entered. To avoid postoperative bulging, it is best to keep the incision within a single dermatome.

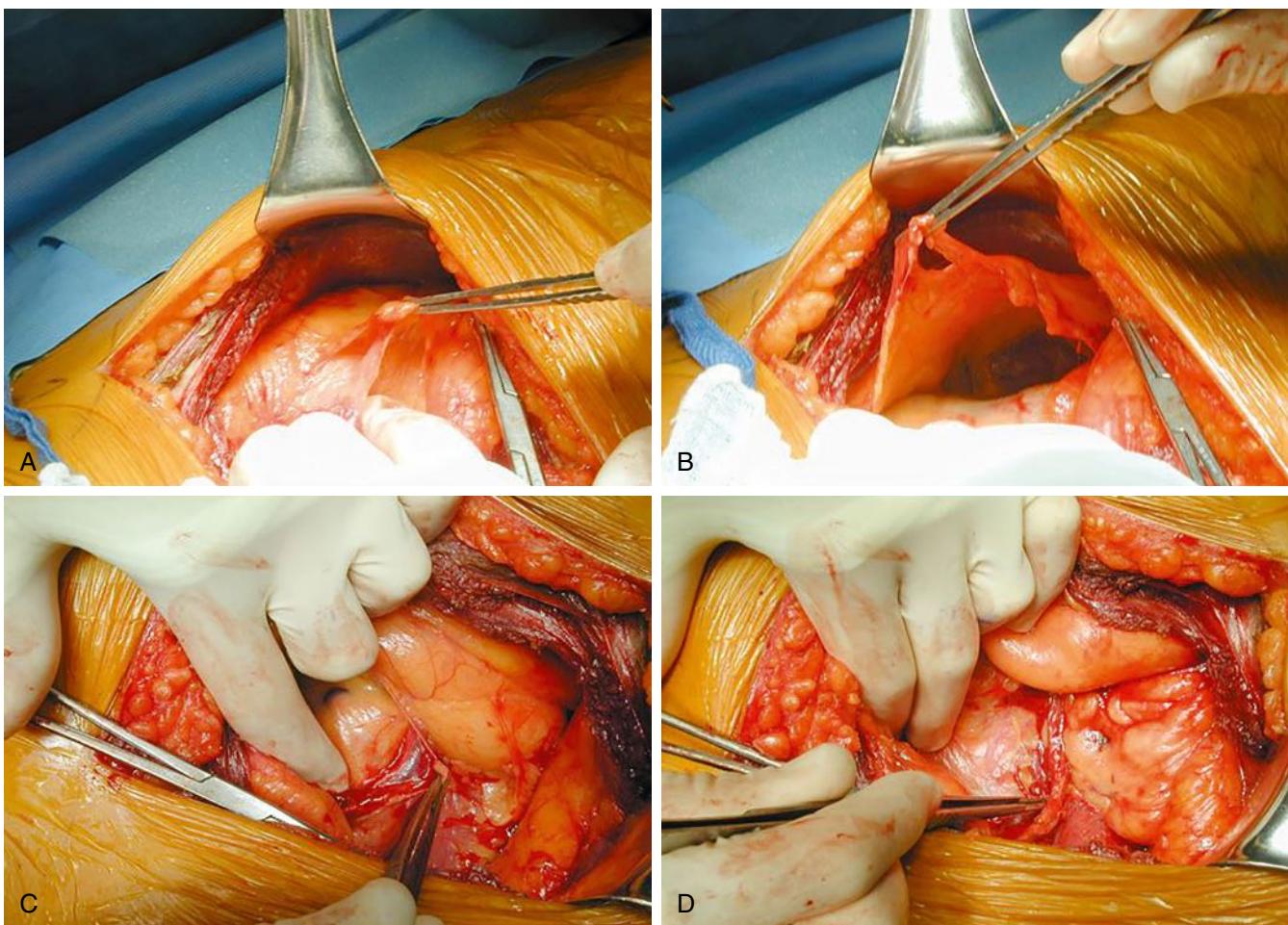


Figure 55.12 Dissection of the Retroperitoneal Space. (A) and (B) demonstrate the plane between the pre-peritoneal fat and pro-peritoneal fat. Developing this plane will guide the surgeon down the aorta. The gonadal vessels and ureter can then be reflected posteriorly (C,D) while the peritoneal contents are retracted anteromedially. This allows the left kidney to remain in its anatomic position while still exposing the abdominal aorta.

Dissection

The dissection is performed in a similar fashion to the abdominal portion of a thoracoabdominal exposure with the following exceptions. The anterior rectus sheath is divided after dissecting through the subcutaneous tissue; however, care should be taken not to divide the rectus muscle fibers to reduce hernia formation.⁷ If exposure of the right common iliac artery is needed, division of the posterior rectus sheath can be performed, leaving the muscle fibers of the rectus intact. Craniocaudally the oblique musculature is again divided down to the peritoneal cavity, keeping this division within a single dermatome.

Once the retroperitoneal space is created, the surgeon can continue the dissection in the pre-peritoneal space, the plane used in a thoracoabdominal incision, ultimately sweeping the contents off of the psoas muscle. Care should be taken to stay in the plane anterior to the psoas muscle, avoiding tearing the psoas fascia. The genitofemoral and ilioinguinal nerves should be identified and protected. There is a tendency to go behind the psoas muscle, which leads to increased bleeding and injury to the ilioinguinal and genitofemoral nerves. A self-retaining retractor is placed and the anterior abdominal wall and viscera are held to the right.

Alternatively, the plane between the pre-peritoneal fat and pro-peritoneal fat can be developed (Figs. 55.12 and 55.13). Developing this space allows the surgeon to sweep the pre-peritoneal fat and the peritoneal contents medially while leaving the posterior pro-peritoneal contents in place, ultimately leaving Gerota's fascia and the left kidney undisturbed in their anatomic location. This approach reduces manipulation of the left kidney but limits the amount of cranial exposure that can be achieved. In both scenarios, the abdominal aorta is encountered, and the para-aortic fat is dissected free. When the pro-peritoneal fat is left in place, the gonadal vein and ureter should be identified to ensure it is not lifted medially with the peritoneal contents but rather left in their anatomic location. In cases where the kidney is left in its anatomic location, the gonadal vein can be ligated at its junction with the left renal vein to allow further and safe retraction.

Once the aorta is encountered, the dissection of the infrarenal and paravisceral segments of the aorta can be completed as described in the thoracoabdominal section. It is best to avoid the lymphatic tissue postero-lateral to the infrarenal aorta as it tends to create bleeding, which is difficult to control. The