

AGA Technical Review on Intestinal Ischemia

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Practice Economics Committee. The paper was approved by the committee on September 25, 1999, and by the AGA Governing Board on November 25, 1999.

There are no type I data (randomized controlled trials) and few type II data (nonrandomized controlled trials, collaborator case-controlled trials with historical controls), but a plethora of type III data (descriptive studies, blind experience, and expert reports)¹ that the clinician can use to help diagnose and treat patients with intestinal ischemia. Moreover, in view of the relative infrequency of these conditions and the broad spectrum of ischemic injury to the intestinal tract, it is unlikely that type I or type II trials will be forthcoming. This review is structured in the form of responses to the questions most commonly asked about the various forms of intestinal ischemia, including acute mesenteric ischemia (AMI), chronic mesenteric ischemia (CMI), and colonic ischemia (CI).

Acute Mesenteric Ischemia

What Physician-Dependent Factor Is Most Important in Determining the Outcome of an Episode of AMI?

AMI can result from emboli, arterial and venous thrombi, or vasoconstriction secondary to low-flow states. For each of these conditions, there are different reasons for needing practice guidelines to optimize patient treatment. In clinical series of AMI reported over the last 15 years, mortality rates remain as high as they did more than 70 years ago and average 71%, with a range of 59%–93% (Table 1). These dismal results persist despite progress in our understanding of the pathophysiology, diagnosis, and treatment of AMI that has made it possible to save the lives of most patients and salvage the intestines of patients with AMI. Thus it is both paradoxical and tragic that the relatively poor clinical results do not reflect the advances that have been made. Diagnosis before the occurrence of intestinal infarction is the most important factor in improving survival for patients with AMI. Thus the objectives of any guideline for the management of AMI are identification of patients who require prompt and aggressive evaluation and delineation of the optimal form of therapy for each patient.

Although there is substantial evidence that mortality rates for the various causes of AMI are different, e.g., mesenteric venous thrombosis is much less lethal than superior mesenteric artery embolus, this factor is not within the physician's control. It is logical that early diagnosis, especially before bowel infarction, would im-

Table 1. Mortality Rates for AMI

Study (yr)	No. of patients	Mortality rate (%)
Braun ² (1985)	52	64
Clavien et al. ³ (1987)	81	83
Cohen Solal et al. ⁴ (1993)	30	67
Finucani et al. ⁵ (1989)	32	66
Georgiev ⁶ (1989)	175	93
Inderbitzi et al. ⁷ (1992)	100	68
Kach and Largiader ⁸ (1989)	45	60
Koveker et al. ⁹ (1985)	39	85
Levy et al. ¹⁰ (1990)	92 ^a	59
Mishima ¹¹ (1988)	162	65
Ritz et al. ¹² (1997)	141	71
Voltolini et al. ¹³ (1996)	47	72
Zan et al. ¹⁴ (1993)	32	72

^aPatients with NOMI excluded.

prove survival. This premise is supported by several retrospective studies (Table 2) in which diagnosis within 24 hours of presentation to a physician or before any significant bowel infarction occurred resulted in markedly improved survival. In a report from Madrid of 21 patients with superior mesenteric artery embolus, intestinal viability was achieved in 100% of patients if the duration of symptoms was less than 12 hours, in 56% if it was between 12 and 24 hours, and in only 18% if symptoms were more than 24 hours in duration before diagnosis.²⁰

Which Patients Require Early and Aggressive Evaluation for AMI?

Patients at risk who have abdominal pain severe enough to call to the attention of a physician and whose pain persists for more than 2 or 3 hours should be evaluated. Patients at risk have been identified in retro-

Abbreviations used in this paper: AMI, acute mesenteric ischemia; APC, activated protein C; CI, colonic ischemia; CMI, chronic mesenteric ischemia; CT, computed tomography; MRI, magnetic resonance imaging; MVT, mesenteric vein thrombosis; NOMI, nonocclusive mesenteric ischemia; PTMA, percutaneous transluminal mesenteric angioplasty; rtPA, recombinant tissue plasminogen activator; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SMVT, superior mesenteric venous thrombosis; SQUID, superconducting quantum interference device.

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0016-5085/00/\$10.00
doi:10.1053/gg.2000.7031

Table 2. Studies Showing the Importance of Early Diagnosis of AMI on Survival

Study (yr)	No. of patients	Mortality (%)		Mortality (%)	
		No gangrene	Gangrene	Sxs < 24 h	Sxs > 24 h
Batellier and Kieny ¹⁵ (1990)	65	25	68	—	—
Boley et al. ¹⁸ (1981)	47	—	—	57	73
Inderbitzi et al. ⁷ (1990)	83	—	—	0 ^a	88
Kieny ¹⁶ (1990)	98	26	71	—	—
Lazaro et al. ¹⁷ (1986)	23	25	75	—	—
Levy et al. ¹⁰ (1990)	92	31	73	—	—
Ritz et al. ¹² (1997)	141	—	—	44 ^b	92
Vellar and Doyle ¹⁹ (1977)	52	—	—	54	95

Sxs, symptoms.

^a<12 hours, mortality = 17%.

^b<12 hours, mortality = 0%.

spective studies as those older than 50 years with congestive heart failure, cardiac arrhythmias, recent myocardial infarction, hypovolemia, hypotension, or sepsis.²¹ More recently, intestinal ischemia, especially nonocclusive mesenteric ischemia (NOMI), has been reported increasingly after cardiac surgery²² and dialysis.²³ A history of previous arterial emboli, vasculitis, deep vein thromboses, hypercoagulable states (protein C and S deficiencies, anti-thrombin III deficiency, and activated protein C [APC] resistance, among others), or chronic postprandial pain places a patient in the high-risk group. Despite these broad categories, reported series have included patients younger than 50 years old and many patients without any of the conditions that suggest increased risk. Hence, it is important to consider and pursue the diagnosis of AMI in any patient who has the classic early finding of severe abdominal pain out of proportion to the physical findings.

Are There Any Noninvasive Studies That Establish or Exclude the Diagnosis of AMI?

Based on experimental studies, numerous serum markers and noninvasive imaging techniques have been proposed for the diagnosis of AMI.²⁴ Simply stated, no serum marker is sensitive or specific enough to establish or exclude the diagnosis. Moreover, elevations in the levels of serum markers most suggestive of intestinal ischemia usually occur only after transmural bowel infarction develops and therefore cannot be used to diagnose AMI in its early stages, when improved survival would be possible. Any useful serum marker must be detectable in a rapidly performed assay that would not delay further evaluation and treatment. The assays of some of the most promising experimental markers, e.g., intestinal fatty acid-binding protein, currently take more than 12 hours and hence are not of practical value.

A number of other noninvasive techniques have been explored.

Plain x-ray films of the abdomen. Plain x-ray films of the abdomen have been part of almost all protocols for the diagnosis of AMI. A normal plain x-ray film does not exclude the diagnosis of AMI, and ideally, these studies should show no abnormalities if an early diagnosis is to be made. Plain film findings with AMI usually are nonspecific, late, and associated with a high mortality rate.¹² In the study by Ritz et al.,¹² patients with normal plain radiographic findings had a mortality rate of 29%, whereas the mortality rate of those with abnormal findings (ileus of varying degree) was 78%. The primary role of abdominal plain x-ray films is to exclude other identifiable causes of abdominal pain, e.g., perforated ulcer, in a patient suspected of having AMI.

Duplex sonography (Doppler ultrasonography). Several groups have studied the efficacy of duplex sonography in the diagnosis of AMI or CMI. This test was found to be highly specific (92%–100%) for identification of occlusions or severe stenoses of the splanchnic vessels but to have a sensitivity of only 70%–89%.^{25,26} Unfortunately, duplex sonography is of no value in detecting emboli beyond the proximal main vessel or in diagnosing NOMI. Moreover, identification of significant arterial stenosis does not establish the diagnosis of intestinal ischemia because total occlusion of two or even all three splanchnic vessels can be present in asymptomatic patients.

Computed tomography. Standard computed tomography (CT) has been used in the detection of intestinal ischemia with varying results. As on plain radiography of the abdomen, most abnormalities on CT associated with AMI are nonspecific and occur late in the course of the disease. Highly suggestive findings for AMI, including portal venous gas and pneumatosis intestinalis, are seen only after gangrene has developed. A retrospective comparison of plain x-ray films of the abdomen and abdominal CT scans in 23 patients with

proven intestinal infarction showed specific findings in 30% and 39%, respectively.²⁷ Both abdominal plain x-ray films and CT scans showed only nonspecific abnormalities in 35% of patients with infarcted bowel, again showing that such studies cannot be used to exclude the diagnosis of AMI even after infarction.²⁷ In another study on the value of CT scanning in patients with suspected ischemia or infarction, a specific diagnosis was made in only 26%.^{28a}

In the study with the highest sensitivity (64%) for CT diagnosis of AMI,^{28b} the investigators considered the presence of just one of several findings (arterial or venous thrombi, intramural or portal venous gas, focal lack of bowel wall enhancement after intravenous contrast, or hepatic or splenic infarction) as a "positive" study. Most of these signs are either late or inferential. As with duplex sonography, proponents of CT agree that angiography is superior to CT for the identification of mesenteric artery branch occlusions or NOMI.

In contrast to its limited role in the diagnosis of AMI caused by superior mesenteric artery (SMA) occlusion or NOMI, CT diagnosis of mesenteric vein thrombosis (MVT) has proven more valuable. The association of an occluded superior mesenteric vein (SMV) and other findings common to all forms of mesenteric ischemia has permitted the diagnosis of mesenteric ischemia from MVT in symptomatic individuals. Thrombosis of the SMV without associated bowel abnormalities has been shown by CT in many asymptomatic patients. Such studies have broadened our understanding of the whole spectrum of MVT, which ranges from chronic MVT with no symptoms to acute MVT with bowel infarction. Although CT could be considered the primary diagnostic tool for patients with suspected AMI from MVT, its general use for those suspected of having any form of AMI is not supported in the literature. We have suggested that a contrast-enhanced CT scan should be the initial imaging study in patients with abdominal pain who have a history of deep vein thrombosis or thrombophlebitis or a family history of a hypercoagulable state.²⁹ A diagnosis was made by CT in all patients with acute MVT and 93% of those with chronic thrombosis in a series of 72 patients from the Mayo Clinic.³⁰ In the same series, the diagnosis was made by angiography in patients in whom it was used. In another series, CT established the diagnosis of splenoportal or SMV thrombosis in 6 patients with acute symptoms but no abdominal signs.³¹ After institution of intravenous anticoagulation therapy, these patients were evaluated twice weekly with sonography, CT, or both until recanalization occurred. Thus, CT can be used both to diagnose and to monitor patients treated nonsurgically. Spiral CT and CT angiography may be even more useful

for evaluation of the splanchnic vessels, although experience with these techniques is limited.^{32,33}

Magnetic resonance imaging. Magnetic resonance imaging (MRI) angiography with and without gadolinium enhancement has been evaluated experimentally and clinically for the diagnosis of intestinal ischemia. In the only clinical study,³⁴ high sensitivity and specificity were found for severe stenoses or occlusion of the origins of the celiac axis and SMA. However, this modality is limited in identification of more peripheral occlusions and NOMI.

Other techniques. A variety of techniques, including radioisotope studies, tonometry, superconducting quantum interference device (SQUID), and endoscopy, have been studied experimentally and clinically, although experience with them is too limited to validate their reliability and usefulness.

What Is the Role of Angiography in the Diagnosis and Management of AMI?

Selective mesenteric angiography is considered by most authorities on vascular disorders of the bowel as the gold standard for the diagnosis of AMI.^{8,20,35-50} Recognition that the diagnosis of AMI before bowel ischemia becomes irreversible is the most important factor in improving patient survival, and recognition that only angiography or surgery enables such early diagnosis has led experts to view angiography as a cornerstone in the evaluation of patients with abdominal pain who are at high risk for AMI.

Opponents of routine angiography for such patients point to several problems with this approach. First, difficulties in performing angiography in critically ill patients may make the study impractical and contribute to inordinate delays in surgery. Second, the large number of negative results in examinations performed to identify patients with AMI early in the course of the disease is considered by some to offset the value of the study. Third, the most serious potential drawback is the possible critical delay in the surgical correction of vascular insufficiency because angiography is not readily available. Proponents of angiography accept that the large number of negative angiography results, with their low risk of complications, is essential if diagnoses are to be made early enough to improve survival. All agree, however, that prompt laparotomy is indicated in patients with suspected AMI in whom expeditious angiography is not available. A decreased mortality rate has been demonstrated clearly in a number of reported series in which routine angiography has been used (Table 3). The sensitivity (74%–100%) and specificity (100%) in these series

seem to justify the reliance placed on this test. Although the complication rate of angiography in this setting is not available from most reports, no such complications contributed to patient mortality in our series.⁵¹

More controversial is the need for angiography in a patient with suspected AMI and signs of an acute abdomen. Because signs of peritonitis usually indicate infarcted bowel, the most compelling reason for angiography, i.e., diagnosis while the effects of intestinal ischemia are still reversible, is no longer a consideration. Hence, some investigators recommend going directly to laparotomy.⁴³ Supporters of angiography in this setting cite the following as reasons to perform this study: diagnosis of AMI and its cause, the means to administer intra-arterial vasodilators for NOMI and as part of the therapy for occlusive disease, provision of a "roadmap" for revascularization procedures, and access for serial postoperative angiographic studies. An especially important advantage of knowing preoperatively if AMI is occlusive or nonocclusive is the ability to avoid any dissection around the SMA in patients with the latter; such dissection could worsen vasoconstriction.

What Course of Therapy Is Indicated If Results of Angiography Are Positive for AMI?

If it shows an SMA embolus. Various therapeutic approaches have been proposed for SMA emboli depending on (1) the presence or absence of peritoneal signs, (2) whether the embolus is partially or completely occluding, and (3) whether the embolus is in the SMA above the origin of the ileocolic artery (i.e., major embolus) or more distally in the SMA or in one of its branches (i.e., minor embolus). Surgical revascularization, intra-arterial perfusion with a thrombolytic agent, intra-arterial infusion of vasodilators, and simple systemic anticoagulation³⁹ have all been used.

There is uniform agreement that exploratory laparotomy is mandatory when signs of peritonitis are present

and that embolectomy and resection of any infarcted bowel should be performed as necessary. In the absence of peritoneal signs, the standard treatment for major SMA emboli remains surgical embolectomy. However, thrombolytic agents, e.g., streptokinase, urokinase, and recombinant tissue plasminogen activator (rtPA) have been used with some success as noted in multiple case reports⁵⁴⁻⁶⁶ and five small series⁶⁷⁻⁷¹ (Table 4). A review of that experience suggests that thrombolytic therapy is most likely to be successful when the thrombus is partially occluding, or is in one of the branches of the SMA or in the main SMA distal to the origin of the ileocolic artery, and the study is performed within 12 hours of the onset of symptoms.

Infusion of papaverine into the SMA has been used as the sole therapy—without surgery—in highly selected patients with major emboli. Criteria for the use of papaverine in this manner are (1) absence of peritoneal signs, (2) a compelling medical reason for the patient not to undergo surgery, and (3) good perfusion of the vascular bed distal to the embolus after a bolus injection of a vasodilator, e.g., tolazoline.¹⁸ Experience with this technique is limited.

In the absence of peritoneal signs, minor SMA emboli have been treated successfully with thrombolytic agents,^{54-66,61-71} intra-arterial papaverine,^{36,51} or anticoagulants without the need for surgery.

The most controversial aspect of the management of SMA emboli is the importance and treatment of associated vasoconstriction. There is ample experimental and clinical evidence that vasoconstriction of both the unobstructed and obstructed branches of the SMA occurs with an SMA embolus even after the embolus has been removed.^{36,50,51,72,73} Such vasoconstriction resolves spontaneously if the embolus is removed soon after it develops. However, if the vasoconstriction has existed long enough, it can become persistent⁷⁴ (Figure 1). Recognition of persistent vasoconstriction has prompted

Table 3. Studies in Which Mesenteric Angiography Was Used Routinely in Diagnosis and Management of AMI

Study (yr)	No. of patients	Positive (%)	Sensitivity (%)	Specificity (%)	Mortality (%)
Boley et al. ⁵¹ (1977)	50	70	94	100	46 ^a
Boos ⁵³ (1992)	62	95	100	—	53
Bottger et al. ⁴⁵ (1994)	46	—	74	—	—
Clark and Gallant ³⁶ (1984)	56	48	100	100	52
Czerny et al. ⁵² (1997)	70	—	92	—	30 ^b
Kaufman et al. ³⁹ (1977)	11	100	100	—	18 ^c

^aNine of 10 patients without peritoneal signs survived, but only 10 of 25 patients with peritoneal signs survived; 17 of 19 survivors lost no or <3 ft of intestine.

^bSensitivity based on 102 cases.

^cReport was limited to patients with diagnoses within 24 hours of onset of symptoms; 2 patients with extensive gangrene died, whereas all 9 patients without extensive gangrene survived.

Table 4. Case Reports and Small Series of Use of Thrombolytic Agents for SMA Emboli

Study (yr)	No. of patients	Occlusion		Location		Drug			Outcome
		Partial	Total	Central	Peripheral	SK	UK	rtPA	
Badiola and Scoppetta ⁵⁴ (1997)	1			+			+		Successful
Bonardelli et al. ⁵⁵ (1994)	1		+	+					Embolectomy, resection
Boyer et al. ⁵⁶ (1994)	1	+		+				+	Successful
Flickinger et al. ⁵⁷ (1983)	1		+	+		+			Embolus lysed, patient died of CHF
Gallego et al. ⁶⁷ (1996)	2			1	1		+		Successful by 4 h
Hillers et al. ⁵⁸ (1990)						+			
Hirota et al. ⁵⁹ (1997)	1						+		Successful
Kwauk et al. ⁶⁰ (1996)	1				+	+			Successful
McBride and Gaines ⁶¹ (1994)	1					+			Successful
Pillari et al. ⁶² (1983)	1		+	+		+			Successful by 36 h
Ramirez et al. ⁶³ (1990)	1								Successful
Regan et al. ⁶⁴ (1996)	1	+		+			+		Successful
Rodde et al. ⁶⁵ (1991)	1		+		+		+		Successful
Schoenbaum et al. ⁶⁸ (1992)	4	2	2				+		Resection needed in 1 patient
Sicard et al. ⁶⁹ (1984)	2								Successful
Simo et al. ⁷⁰ (1997)	10						+		Embolysis, 90%; clinical success, 70%; laparotomy, 30%
Turegano Fuentes et al. ⁷¹ (1995)	2			1	1		+		
Vujic et al. ⁶⁶ (1984)	1					+			Successful by 30 h

SK, streptokinase; UK, urokinase; rtPA, recombinant tissue plasminogen activator; CHF, congestive heart failure.

some investigators to recommend routine use of intra-arterial papaverine in all patients with SMA emboli.^{21,75,76} No hard data support this approach, but the best survival rates have been achieved in series in which papaverine has been used routinely.^{36,51} In series that included only patients who had early embolectomy without papaverine infusion, equally good results were obtained, suggesting that persistent vasoconstriction had not yet developed.³⁹ In other series in which papaverine was not used,⁸ worse results were reported after embolectomy with and without intestinal resection than when resection alone was performed. Although these findings have been attributed to thrombosis at the arteriotomy site, this complication occurred infrequently when post-operative papaverine was infused. It is likely that persistent vasoconstriction was responsible for failure to restore arterial perfusion to the bowel after embolectomy and for progression from bowel ischemia to infarction even after SMA blood flow had been restored. Although many investigators^{36,51,74,75} recommend intra-arterial infusion of papaverine before and after embolectomy, this approach is not practiced universally.

If it shows SMA thrombosis. Problems in interpretation of angiographic demonstration of SMA occlusion are (1) differentiation of an embolus from a thrombosis (usually based on the appearance and location of the occlusion) and (2) determination of whether the occlusion is new or long-standing. Demonstration of collaterals and late visualization of the SMA indicate the latter and suggest that acute abdominal pain is unrelated to the SMA lesion.

If a diagnosis of acute thrombosis is made, emergency

surgical revascularization is recommended almost universally. Although thrombolytic therapy and percutaneous angioplasty have been recommended by some investigators for CMI and SMV thrombosis, there are few reports of the use of these modalities for SMA thrombosis.

If it shows NOMI. There is little controversy over angiography as the only way to diagnose NOMI before intestinal infarction occurs. Moreover, there is general agreement that when NOMI has been identified, infusion of a vasodilator, most commonly papaverine hydrochloride, into the SMA can relieve the vasoconstriction and prevent further ischemic damage to the bowel. In series in which angiography was used, this approach reduced mortality rates of NOMI from historical levels of 70% to greater than 90% to 0% to 55%.^{36,51,77} Although these series are relatively small (a total of 33 patients), there are a number of other isolated reports of survival with and without the need for bowel resection after papaverine infusion. Early diagnosis by angiography followed by intra-arterial papaverine infusion is the best means of improving survival and maintaining intestinal integrity (Figure 2). Patients with peritoneal signs and the angiographic diagnosis of NOMI undergo laparotomy and receive intra-arterial infusions of papaverine before, during, and after surgery as indicated.

If it shows mesenteric venous thrombosis. Although superior mesenteric venous thrombosis (SMVT) can be diagnosed by mesenteric angiography, it is more common that the diagnosis is established by CT or laparotomy. Treatment of patients with SMVT is discussed below.

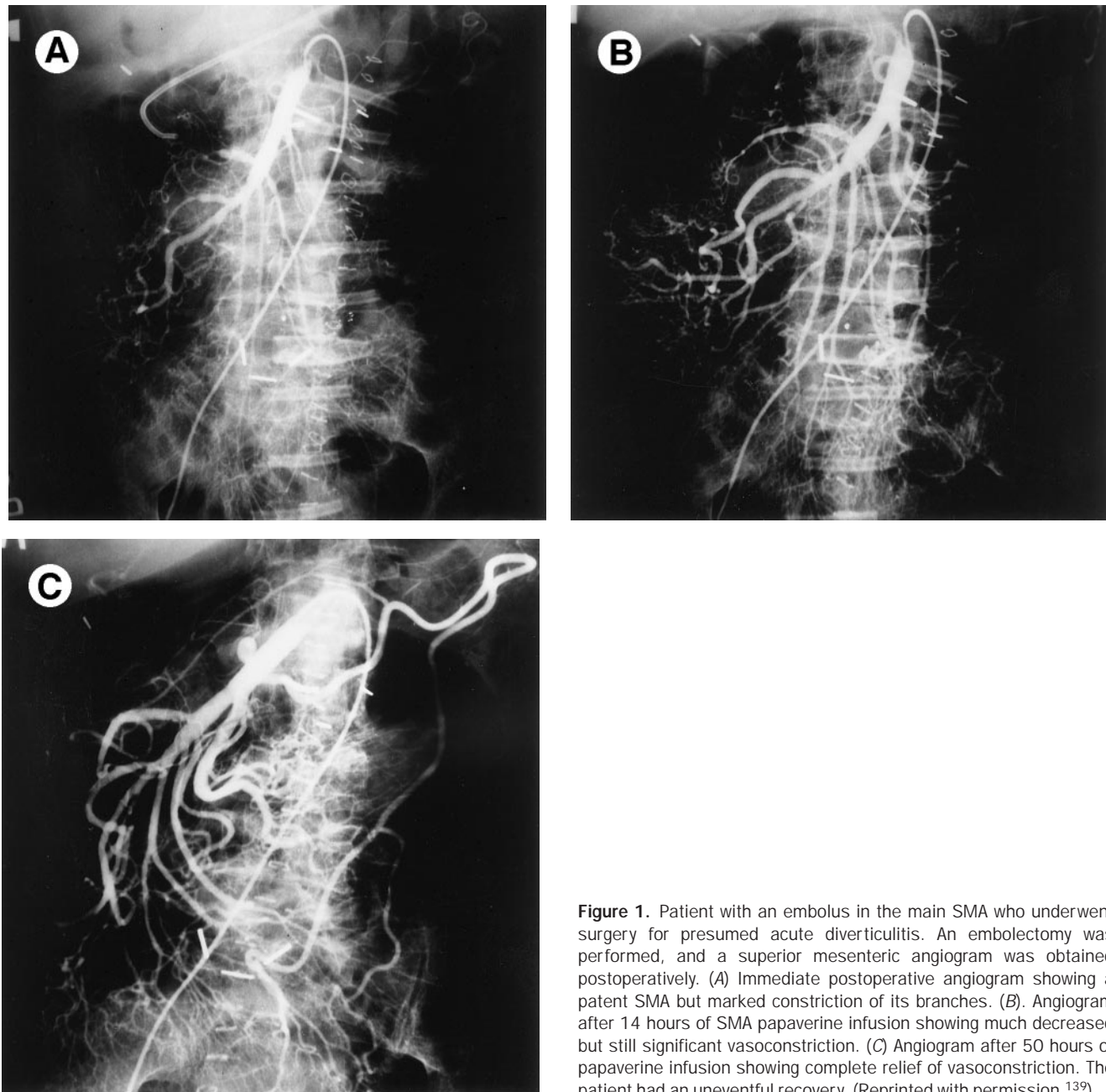


Figure 1. Patient with an embolus in the main SMA who underwent surgery for presumed acute diverticulitis. An embolectomy was performed, and a superior mesenteric angiogram was obtained postoperatively. (A) Immediate postoperative angiogram showing a patent SMA but marked constriction of its branches. (B) Angiogram after 14 hours of SMA papaverine infusion showing much decreased but still significant vasoconstriction. (C) Angiogram after 50 hours of papaverine infusion showing complete relief of vasoconstriction. The patient had an uneventful recovery. (Reprinted with permission.¹³⁹)

What Is the Proper Approach to the Diagnosis and Treatment of a Patient With Suspected SMVT?

Most patients with SMVT are initially believed to have some form of AMI and not specifically MVT. Hence they are treated as described in the preceding sections. In patients with a personal or family history of a hypercoagulable state, (recurrent) thrombophlebitis, or deep vein thrombosis, however, we suggest a contrast-enhanced CT scan as the initial diagnostic study. In asymptomatic individuals in whom the diagnosis has been made on a CT scan obtained for reasons other than abdominal pain, either no therapy or a 3–6-month course of anticoagulation is reasonable; there are no studies to aid in this

therapeutic decision. In symptomatic patients in whom an acute thrombosis of the SMV is diagnosed, either by CT scan or angiography, treatment is determined by the presence or absence of peritoneal signs. As with all patients with AMI, signs of peritonitis mandate laparotomy and resection of infarcted bowel. In patients with SMVT, immediate heparinization has been shown to diminish recurrence and progression of thrombosis and to improve survival.^{30,78–82} In the absence of peritoneal signs, immediate institution of anticoagulant therapy with heparin followed by clinical observation and administration of Coumadin may be all that is necessary.^{30,80} If signs of peritonitis develop, prompt surgery is indicated.

A routine “second-look” procedure (re-exploration

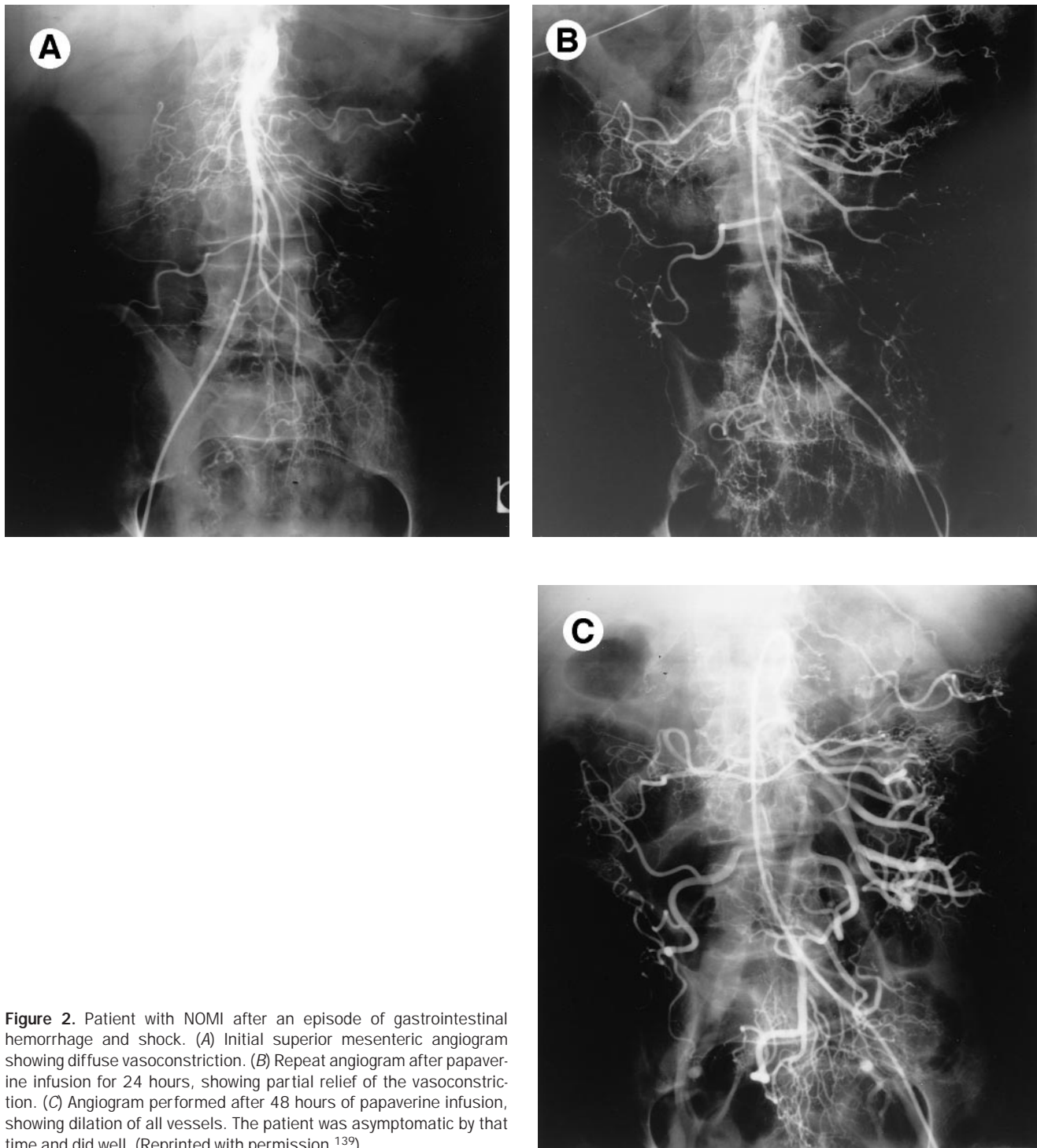


Figure 2. Patient with NOMI after an episode of gastrointestinal hemorrhage and shock. (A) Initial superior mesenteric angiogram showing diffuse vasoconstriction. (B) Repeat angiogram after papaverine infusion for 24 hours, showing partial relief of the vasoconstriction. (C) Angiogram performed after 48 hours of papaverine infusion, showing dilation of all vessels. The patient was asymptomatic by that time and did well. (Reprinted with permission.¹³⁹)

within 12–24 hours) has been recommended by some investigators,⁸³ but most authorities^{29,30,84} use this surgery selectively, only when bowel of questionable viability has been left behind.

How Long Should Anticoagulation Be Maintained in a Patient With SMVT?

Again, no studies answer this question definitively, but by convention, patients receive heparin for

7–10 days first, then an oral regimen of Coumadin for 3–6 months.

Thrombolysis has recently been proposed for the treatment of acute SMVT. Thrombolytic agents have been administered successfully in an antegrade fashion via the SMA,^{85–87} retrograde via the internal jugular vein,⁸⁸ and transhepatically via the portal vein.^{89,90} Only a few case reports document application of this technique to SMVT.

What Is the Role of Anticoagulation in Patients With AMI?

As noted above, in patients with acute SMVT, immediate anticoagulation with heparin is indicated regardless of whether the patient requires surgical intervention. However, the precise duration of anticoagulation with heparin or Coumadin has not been defined. For patients with AMI of arterial origin, i.e., SMAE (superior mesenteric artery embolus), NOMI, SMAT (superior mesenteric artery thrombosis), there is consensus that heparinization is indicated but controversy as to when it should be initiated. Some investigators recommend a delay of 48 hours because of the risk of intraluminal bleeding from damaged bowel,¹⁸ whereas other experts believe the benefits of immediate heparinization may offset that danger.⁹¹ Some authorities recommend immediate heparinization if no infarction is present but delay in anticoagulation if intestinal infarction is present.¹⁵ No good data support any of these approaches, but there are reports of patients who were given heparin immediately and developed significant gastrointestinal bleeding. Certain medical conditions, e.g., coagulopathies and atrial fibrillation, may warrant lifelong anticoagulation.

Chronic Mesenteric Ischemia

CMI ("intestinal angina") is characterized by postprandial pain and marked weight loss and is caused by repeated, transient episodes of inadequate intestinal blood flow, usually provoked by the increased metabolic demands associated with digestion. Although CMI is rare and usually does not require emergency therapy, the risks of incapacitation or acute thrombosis of one of the involved vessels are substantial. Because angiographic evidence of partial or complete occlusion of one or more of the major splanchnic vessels is common in the absence of CMI, such findings alone are not sufficient for diagnosis of CMI. There is controversy concerning whether multiple vessels or just the SMA should be revascularized and under what circumstances transluminal angioplasty may suffice. The objectives of this guideline are to help physicians identify patients with CMI and determine the best means of re-establishing adequate intestinal blood flow.

When Should CMI Be Suspected, and How Is It Diagnosed?

Patients with CMI have a syndrome described as "abdominal angina" by Goodman in 1918⁹² and "intestinal angina" by Mikkelsen in 1957.⁹³ This syndrome consists of generalized abdominal pain that occurs shortly after meals and persists for 1–3 hours. Although it is minimal at first, abdominal pain progressively increases

in severity over weeks to months. The association of pain with meals leads to fear of eating, with resultant weight loss. Patients with this clinical picture should be suspected of having CMI, unless another explanation for the abdominal pain is found.

Although many tests have been proposed to establish the presence of CMI, none have proven sensitive and specific enough to be diagnostic. Only one test, provocative balloon tonometry, evaluates the physiological adequacy of intestinal blood flow.⁹⁴ All other tests (precibal and postcibal duplex ultrasonography,⁹⁵ MRI angiography,^{96–98} MRI oximetry,⁹⁹ and intestinal oxygen consumption¹⁰⁰) are indirect measurements of an anatomic limitation of splanchnic blood flow and do not establish the presence or absence of intestinal ischemia. In the absence of any specific, reliable diagnostic test, diagnosis must be based on clinical symptoms, arteriographic demonstration of an occlusive process of the splanchnic vessels, and, to a great measure, exclusion of other gastrointestinal disorders.

In most patients with CMI, at least two of the three splanchnic vessels are either completely obstructed or severely stenosed. In a comprehensive review of reported series of patients with CMI, 91% had occlusion of at least two vessels and 55% had involvement of all three¹⁰¹; 7% and 2% had isolated occlusion of the SMA and celiac axis, respectively.

Although several new diagnostic techniques mentioned above are being evaluated, even their proponents believe selective arteriography is critical to confirm the diagnosis of CMI and to plan therapy, whether it be surgery or interventional radiology.

How Should a Patient With a Diagnosis of CMI Be Treated?

Surgical revascularization has been the method of therapy for most patients with CMI. Since the early 1980s, percutaneous transluminal mesenteric angioplasty (PTMA) alone or with stent insertion has been offered as alternative therapy, but results have been reported only in small numbers of patients. Whether surgery or PTMA is better will be determined by their relative successes in relieving symptoms and the durability of such relief.

The results of surgical revascularization for CMI vary depending on the nature of the operations used, the number of splanchnic vessels revascularized, and whether concurrent operations, e.g., aortic reconstruction, are performed. Surgical treatment for CMI includes both antegrade and retrograde bypass grafting, aortic reimplantation of the SMA, and transarterial and transaortic mesenteric endarterectomy.

The true efficacies of both surgical revascularization and PTMA are difficult to determine because of the

varied criteria used by different investigators to define a successful outcome. Thus, some authors use graft or vessel patency rates, whereas others define success by partial or complete relief of symptoms, recurrence rates, or long-term survival. A representative sample of retrospective reports on surgical revascularization is shown in Table 5. In 614 patients, perioperative mortality rates ranged from 0% to 16%; success rates and recurrence rates ranged from 59% to 100% and 0% to 26.5%, respectively. Most recent series have reported mortality rates toward the lower end of the range, success rates of over 90%, and recurrence rates generally under 10%.

The initial success rates of PTMA are similar to those of surgical revascularization (Table 6). The experience with PTMA is more limited but has been achieved in patients often considered too high-risk for a surgical procedure. Rates of clinical success (relief of symptoms) have varied from 63% to 100% with few mortalities. However, recurrence of symptoms has been much higher than after surgical revascularization, varying from 10% to 67% in the larger series. More recently, intraluminal stenting has been added to PTMA in an attempt to decrease the incidence of recurrent stenoses. The paucity of patients treated in this fashion precludes a conclusion about its long-term value in treatment of patients with CMI.

Based on currently available information and the consensus of investigators, patients with CMI who are otherwise relatively healthy probably should be treated by surgical revascularization; patients at higher risk probably should have an initial attempt at PTMA with or without stenting to relieve symptoms. However, if the use of stents reduces the recurrence rates of PTMA to near

those of surgical revascularization, PTMA may become the method of choice.

What Is the Expected Survival of Patients With CMI Who Have Undergone Successful Surgical Revascularization?

Several long-term studies have shown that patients who survive surgical revascularization have cumulative 5-year survival rates of 81%–86%^{104,106,113} and life table analysis survival rates of 70%–71% ± 11%–15%.^{101,111}

Colonic Ischemia

CI is the most common form of intestinal ischemia and comprises a spectrum of disorders: (1) reversible colopathy (submucosal or intramural hemorrhage), (2) transient colitis, (3) chronic colitis, (4) stricture, (5) gangrene, and (6) fulminant universal colitis. The incidence of CI is underestimated because most patients have mild or transient disease and therefore do not seek medical help or are not hospitalized; hence, they are not included in reported series. Most cases of CI do not have a recognizable cause, although the association with aortic surgery as well as with colon carcinoma and other potentially obstructive lesions is well known. An increasing number of young people are being identified in whom CI is associated with long-distance running, various medications, cocaine use, or one of the newly described coagulopathies. It is apparent that CI may mimic and be confused with other disorders such as inflammatory bowel disease (IBD) and that some cases of CI can be caused by bacterial pathogens. Both cytomegalovirus and *Escherichia coli* O157:H7 damage vascular

Table 5. Representative Results of Series of Surgical Revascularization for CMI

Study (yr)	No. of patients	Procedure mortality (%)	Technical success (%)	Recurrence (%)	Mean follow-up
Beebe et al. ¹⁰² (1987)	10	0	90	0	43 mo
Calderon et al. ¹⁰³ (1992)	20	0	100	0	36 mo
Christiansen et al. ¹⁰⁴ (1994)	53	0	100	40 ^a	—
Cormier et al. ¹⁰⁵ (1991)	103	4	96	5	69 mo
Cunningham et al. ¹⁰⁶ (1991)	74	12	96	10	5 yr
Geelkerken et al. ¹⁰⁷ (1991)	14	7	93	0	11.8 yr
Gentile et al. ¹⁰⁸ (1994)	23	0	100	13	40 mo
Hollier et al. ¹⁰⁹ (1981)	56	9	96	26.5	—
Johnston et al. ¹¹⁰ (1995)	21	0	100	16	5 yr
Kieny et al. ¹¹¹ (1990)	31	3.5	97	13	8.5 yr
McAfee et al. ¹¹² (1992)	58	10	90	10	5+ yr
McCullum et al. ¹¹³ (1976)	33	3	94	3	10 yr
Moawad et al. ¹¹⁴ (1997)	24	4	84	0	29 mo
Rheudasil et al. ¹¹⁵ (1988)	31	6.5	90	10	42 mo
Sandmann et al. ¹¹⁶ (1994)	34	3	59	21.5	1–126 mo
Van Damme et al. ¹¹⁷ (1989)	19	16	84	0	3 yr
Wolf et al. ¹¹⁸ (1998)	10	0	100	0	3 yr

^aAt 5 years.

Table 6. Representative Series of Percutaneous Transluminal Mesenteric Angioplasty for CMI

Study (yr)	No. of patients	Procedure mortality (%)	Technical success (%)	Clinical success (%)	Recurrence (%)	Mean follow-up
Allen et al. ¹¹⁹ (1996)	19	5	95	79	20	39 mo
Birch and Colapinto ¹²⁰ (1982)	2	0	100	100	0	7–11 mo
Golden et al. ¹²¹ (1982)	7	0	86	86	0	28 mo
Hallisey et al. ¹²² (1995)	14	0	84	75	67	2.3 yr
Maspes et al. ¹²³ (1998)	23	0	90	85	18	27 mo
Matsumoto et al. ¹²⁴ (1995)	19	0	79	63	0	25 mo
Odurny et al. ¹²⁵ (1988)	10	10	89	80	63	24 mo
Roberts et al. ¹²⁶ (1983)	4	0	100	100	50	27 mo
Rose et al. ¹²⁷ (1995)	8	13	80 ^a	75	25	37 wk
Simonetti et al. ¹²⁸ (1992)	22	0	95	90	10	24 mo

^aOnly 30% (3 of 10) had technical success according to the conventional angiographic definition of residual stenosis of 30% or less.

endothelium, and toxin produced by *E. coli* O157:H7 produces platelet aggregation, intravascular coagulation, and microangiopathic lesions with fibrin thrombi, all leading to hemorrhagic colitis. In addition, using a peroxidase-labeled antibody to whole *E. coli* O157:H7, investigators have shown the presence of this organism in 2 of 11 paraffin-embedded sections from patients with histologically proven ischemic colitis.¹²⁹ Despite the increasing awareness of CI and its varied presentations, many cases are misdiagnosed. The objectives of this guideline are to help identify patients with CI and to detail the proper management of CI in its varied forms.

The initial step in diagnosis of CI is suspicion of the presence of the disease. CI is frequently observed (1) after aortic or cardiac bypass surgery; (2) in association with certain systemic conditions, including vasculitides (e.g., systemic lupus erythematosus, periarteritis nodosum), infections (e.g., cytomegalovirus, *E. coli* O157:H7),¹²⁹ coagulopathies (e.g., protein C and S deficiencies, anti-thrombin III deficiency, APC resistance); (3) in association with use of various medications (e.g., oral contraceptives) or illicit drugs (e.g., cocaine); (4) after strenuous and prolonged physical exertion (e.g., long-distance running); (5) after any major cardiovascular episode accompanied by hypotension; and (6) with obstructing or potentially obstructing lesions of the colon (e.g., carcinoma, diverticulitis).

Most patients with CI do not have any identifiable, specific, and precipitating cause for CI. However, any patient who has one or more of the above conditions and develops mild-to-moderate abdominal pain, diarrhea, or lower intestinal bleeding with minimal-to-moderate abdominal tenderness should be investigated for CI.

What Diagnostic Tests Should Be Used to Evaluate a Patient for CI?

Barium enema was the first method used to diagnose CI. Demonstration of the classic early findings of “thumbprinting” and pseudotumors suggests the

presence of CI, but serial studies showing either complete healing or evolution to ulcers or segmental colitis are required to confirm the diagnosis. Over the last 25 years, colonoscopy has replaced barium enema as the most common diagnostic tool and not only allows direct visualization of the mucosa, but has the additional benefit of tissue sampling.¹³⁰ With the rare exception of mucosal gangrene, however, biopsy findings usually are not helpful and show only nonspecific abnormalities.¹³¹

Mesenteric angiography usually is not indicated in the evaluation of CI, because by the time of presentation, colon blood flow has returned to normal. Angiography may be indicated when the diagnosis of AMI also is being considered, either because only the right side of the colon is affected or because the patient has more severe abdominal pain or more severe physical findings than are usual for CI.

When the clinical presentation does not allow a clear distinction between CI and AMI and plain x-ray films of the abdomen do not show the characteristic thumbprinting pattern of CI, an air enema is recommended. The submucosal edema and hemorrhage that produce the thumbprints can be demonstrated against the column of air. If no thumbprinting is seen, or thumbprints are identified only in the ascending colon, then mesenteric angiography is suggested to exclude occlusive disease of the SMA.

Despite the presence of characteristic findings of CI on each of the above tests, early and repeated clinical evaluation of patients and serial roentgenographic or endoscopic studies of the colon usually are necessary to establish the diagnosis of CI.

How Should a Patient With CI Be Treated?

Treatment varies with the severity of the disease presentation. Most cases of CI resolve spontaneously and do not require specific therapy; such patients have what is called “reversible ischemic colopathy” or “transient ischemic colitis.”¹³¹ When patients with severe or continuing

symptoms must be hospitalized, general supportive measures, bowel rest, and correction of possible precipitating conditions are recommended. The use of antibiotics, the role for corticosteroids, and the need for and timing of surgery are more controversial.

What Is the Role of Antibiotics in CI?

Most authorities recommend the routine use of antibiotics in all patients with moderate or severe acute presentations of CI. However, there is no clinical evidence of beneficial effects of such therapy. The recommendation is based on several old experimental studies¹³²⁻¹³⁴ showing reduction in the severity and extent of bowel damage when antibiotics were given before or during an ischemic event. More recently, antibiotics have resulted in prolonged survival after intestinal ischemia in rats.¹³⁵ Moreover, antibiotics offer theoretic protection against bacterial translocation, which has been shown to occur with the loss of mucosal integrity.^{136,137} The progression of ischemic damage to gangrene is unpredictable and is another reason for the use of antibiotics at presentation.

What Is the Role in CI of Corticosteroids and Other Agents Conventionally Used to Treat IBD?

The only potential role in CI for the agents used to treat IBD is in treatment of patients with chronic ischemic colitis. However, no published experience supports the use of local or systemic corticosteroids, sulfasalazine, and aminosalicylates or fatty acid enemas to treat ischemic colitis. Furthermore, the use of systemic corticosteroids may potentiate ischemic damage¹³⁸ and predispose the patient to colonic perforation.

When Is Surgery Indicated in Patients With CI?

Indications for surgery are listed in Table 7.

The presence of peritoneal signs in a patient with acute onset of CI indicates gangrene or perforation and is a clear mandate for exploratory laparotomy. Similarly, massive bleeding, while rare in CI, usually is an indication for surgery. Patients with universal fulminant ischemic colitis usually appear toxic and are unresponsive to medical therapy, requiring early surgical intervention with subtotal colectomy.

Patients who have an acute episode of CI with evolution to a segmental colitis pattern and whose symptoms persist for more than 2-3 weeks or who have a protein-losing colopathy usually are best treated by segmental colectomy. Attempts to treat such patients nonsurgically often result in perforation or inanition. A less recognized indication for surgery is the development

Table 7. Indications for Surgery in Colonic Ischemia

Acute indications
Peritoneal signs
Massive bleeding
Universal fulminant colitis with or without toxic megacolon
Subacute indications
Failure of an acute segmental ischemic colitis to respond within 2-3 weeks with continued symptoms or a protein-losing colopathy
Apparent healing but with recurrent bouts of sepsis
Chronic indications
Symptomatic colon stricture
Symptomatic segmental ischemic colitis

of recurrent sepsis in a patient who has symptomatically recovered from an acute episode of CI. Such patients usually have a short segment of unhealed bowel that is the source of sepsis; resection of this segment is curative.

Colon stricture after an episode of CI may be asymptomatic or even resolve over months to years. Surgery is indicated only when an ischemic stricture produces symptoms; in such cases, segmental resection is adequate. Transendoscopic dilation of an ischemic stricture is an alternative to surgery, albeit an unproven one. Chronic segmental ischemic colitis is a more controversial indication for surgery. As with other colitides, the decision to abandon medical therapy is a complex one. Because recurrent ischemic episodes are uncommon, resection of the involved segment of colon usually is curative.

Conclusion

The spectrum of ischemic bowel disease is broad, and each type of ischemic injury requires its own unique plan of management. In general, such plans have been developed on the basis of descriptive studies and clinical experience, not on randomized controlled trials or other highly reliable forms of scientific inquiry. However, certain fundamentals seem evident.

First, patients with AMI must be identified early in the clinical course of the disease and treated aggressively if the chance of survival is to be improved. The diagnosis should be suspected when individuals, especially those at high risk for AMI, develop severe and persisting abdominal pain that is disproportionate to their abdominal findings. Such persons should undergo mesenteric angiography if another cause for the pain cannot be found on plain x-ray film studies of the abdomen or CT scan, followed by surgery if angiography shows a vascular cause for the pain. The role of vasodilators is clear for NOMI and is strongly suggested but not as definite for occlusive disease of the SMA. The role of anticoagulants and thrombolytics is evolving.

Second, CMI should be considered in any patient who develops chronic postprandial abdominal pain and weight

loss in whom no diagnosis can be made from the usual diagnostic studies. Mesenteric angiography should demonstrate severe occlusion of at least two of the three splanchnic vessels, although by itself, i.e., in the absence of symptoms, an abnormal angiography result is not sufficient for diagnosis of CMI. Treatment is either surgical or by PTMA with or without stenting. Experience with angiographic treatment modalities is limited, and at present these modalities probably are best reserved for patients at high risk for surgical revascularization.

Third, CI is the most common form of intestinal ischemia and usually has an excellent prognosis; most cases resolve spontaneously. Diagnosis is by colonoscopy or barium enema in an individual with a typical history. Mesenteric angiography plays little role in diagnosing CI, unless only the right side of the colon is affected or the individual has more severe pain than is customarily seen with CI, and hence AMI is suspected. Antibiotics are often used often, despite an absence of good clinical evidence for their benefit. In patients who develop acute ischemic colitis, systemic corticosteroids are best avoided, and there is no evidence supporting the use of conventional agents used to treat IBD. Surgery is indicated acutely for those with peritoneal signs, massive bleeding, or fulminant colitis; subacutely for those who do not improve after 2–3 weeks or who develop recurrent sepsis; and electively in cases of symptomatic ischemic stricture or chronic colitis.

It can only be hoped that future reviews on intestinal ischemia will have the benefit of type I and II data to support treatment recommendations. Until then, a greater awareness of these disorders and critical evaluation of our clinical experiences may allow for earlier diagnoses, prompt therapy, and improved survival.

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The Clinical Practice and Practice Economics Committee acknowledges the following individuals, whose critiques of this review paper provided valuable guidance to the authors: Bruce L. Gewertz, M.D., Leslie W. Ottinger, M.D., and Arvey L. Rogers, M.D.