Mesenteric Ischemia

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MESENTERIC ISCHEMIA IS CAUSED BY BLOOD FLOW THAT IS INSUFFICIENT TO MEET THE METABOLIC DEMANDS OF THE VISCERAL ORGANS. THE SEVERITY OF ISCHEMIA AND THE TYPE OF ORGAN INVOLVED DEPEND ON THE AFFECTED VESSEL AND THE EXTENT OF COLLATERAL-VESSEL BLOOD FLOW.

Despite advances in the techniques used to treat problems in the mesenteric circulation, the most critical factor influencing outcomes in patients with this condition continues to be the speed of diagnosis and intervention. Although mesenteric ischemia is an uncommon cause of abdominal pain, accounting for less than 1 of every 1000 hospital admissions, an inaccurate or delayed diagnosis can result in catastrophic complications; mortality among patients in whom this condition is acute is 60 to 80%.1-3

This article highlights the pathophysiological features, diagnosis, and treatment of ischemic syndromes in the foregut and intestines. The goal of this review is to improve the understanding and management of this life-threatening disorder.

TYPES OF MESENTERIC ISCHEMIA

Arterial obstruction, the most common cause of mesenteric ischemia, has both acute and chronic forms. Acute mesenteric ischemia constitutes a surgical emergency. It is associated with embolic occlusion in 40 to 50% of cases (Fig. 1), with thrombotic occlusion of a previously stenotic mesenteric vessel in 20 to 35% of cases,4 and with dissection or inflammation of the artery in less than 5% of cases. More than 90% of cases of chronic mesenteric ischemia are related to progressive atherosclerotic disease that affects the origins of the visceral vessels; treatment in such cases is focused on elective revascularization to avert the risk of complications and death associated with the development of acute ischemia (Fig. 2).

Mesenteric venous thrombosis, which accounts for 5 to 15% of cases of mesenteric ischemia, results in impaired venous outflow, visceral edema, and abdominal pain. Its causes include primary or idiopathic thrombosis; however, 90% of cases are related to thrombophilia, trauma, or local inflammatory changes that may include pancreatitis, diverticulitis, or inflammation or infection in the biliary system.5 Patients typically have a response to anticoagulation in combination with treatment for the underlying local or systemic processes. Surgical intervention is reserved for patients who are critically ill or whose condition is deteriorating; it is rarely required.

The mesenteric circulation is a high-resistance vascular bed in which impaired regional perfusion owing to vasospasm can develop. The resulting ischemia is referred to as nonocclusive mesenteric ischemia. Although the incidence of nonocclusive mesenteric ischemia may be decreasing as awareness of the condition increases and as supportive therapies improve, it accounts for 5 to 15% of all cases of mesenteric ischemia.6 It is most often associated with cardiac insufficiency.
or low-flow states that occur after cardiac surgery or because of hypovolemia or heart failure, and it is increasingly identified in patients undergoing hemodialysis.\textsuperscript{7} Knowledge of its causes is critical, since misinterpretation of this condition may lead to worsened visceral perfusion and worsened mesenteric ischemia.

### PATHOPHYSIOLOGY

#### MESENTERIC CIRCULATION

The mesenteric circulation is extremely complex. Three primary vessels — the celiac artery, superior mesenteric artery, and inferior mesenteric artery — interconnect through collateral networks between the visceral and nonvisceral circulations. These interconnections ensure that the loss of a single vessel does not lead to catastrophic malperfusion of the viscera.

The acute occlusion of a single vessel (typically the superior mesenteric artery) in acute mesenteric ischemia can result in profound ischemia caused by the loss of blood flow through this key vessel and its collateral vascular network. In contrast, in patients with chronic mesenteric ischemia, additional collateral networks develop over time; symptoms often do not appear until occlusion of two or more primary vessels occurs.

#### CAUSES OF ALTERED CIRCULATION AND MECHANISM OF INJURY

The causes of altered mesenteric circulation are themselves often the result of obstruction or diminished blood flow (Table 1), with a resulting decrease in oxygen delivery to a level that is insufficient to meet the metabolic needs of the visceral organs.\textsuperscript{8} Vasodilatation is the initial response, but prolonged ischemia leads to vasconstriction, which can persist even after intestinal blood flow returns to normal.\textsuperscript{9} This early injury primarily affects the intestinal mucosa and submucosa and potentially impairs mechanisms that prevent the translocation of bacteria from the intestinal lumen.

This sequence of events can result in the activation of systemic inflammatory pathways and ultimately in worsened vasoconstriction,\textsuperscript{10} further regional ischemia, and more extensive injury to the bowel wall.\textsuperscript{9} Without intervention, the damage can progress to full-thickness injury, infarction, and death.

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**Presentation and Initial Evaluation**

**Figure 1. Computed Tomographic Angiography (CTA) in a Patient with Acute Mesenteric Ischemia Caused by an Embolism in the Superior Mesenteric Artery.**

This patient, who had atrial fibrillation and was not receiving anticoagulant therapy, had an acute onset of severe abdominal pain and bloody diarrhea. Panel A shows a sagittal CTA image of a long-segment occlusion of the superior mesenteric artery (arrow). The occlusion was caused by an acute embolism beyond the origin of the superior mesenteric artery. Panel B shows an axial CTA image of complete occlusion of the superior mesenteric artery (arrow) with dilated loops of small bowel.

**History and Physical Examination**

Early attention to the details of the patient’s history and to findings on examination that indicate the presence of mesenteric ischemia is...
critical for timely diagnosis and treatment. In contrast to other vascular disorders, mesenteric ischemia primarily affects women; more than 70% of persons with this disorder are female.

The physician should assess the patient’s records and the results of the examination for any evidence of other atherosclerotic and vascular diseases, including peripheral artery, cerebrovascular, coronary artery, and renovascular disease. In addition, other pulmonary and cardiovascular
conditions must be identified and managed, since they are often coexisting conditions in patients with mesenteric disease and they may limit the available options for revascularization.

**MANIFESTATIONS OF ACUTE MESENTERIC ISCHEMIA**
Patients with acute mesenteric ischemia may initially present with classic “pain out of proportion to examination,” with an epigastric bruit; many, however, do not. Other patients may have tenderness with palpation on examination owing to peritoneal irritation caused by full-thickness bowel injury. This finding may lead the physician to consider diagnoses other than acute mesenteric ischemia. In a patient with abdominal pain of acute onset, it is critical to assess the possibility of atherosclerotic disease and potential sources of an embolus, including a history of atrial fibrillation and recent myocardial infarction. During the examination, the patient’s description of the history and symptoms can be unclear because of changes in mental status, particularly if he or she is elderly.

Differentiation between arterial and venous obstruction is not always simple; however, patients with mesenteric venous thrombosis, as compared with those with acute arterial occlusion, tend to present with a less abrupt onset of abdominal pain. Risk factors for venous thrombosis that should be evaluated include a history of deep venous thrombosis, cancer, chronic liver disease or portal-vein thrombosis, recent abdominal surgery, inflammatory disease, and thrombophilia.

**MANIFESTATIONS OF CHRONIC MESENTERIC ISCHEMIA**
Patients with chronic mesenteric ischemia can present with a variety of symptoms, including abdominal pain, postprandial pain, nausea or vomiting (or both), early satiety, diarrhea or constipation (or both), and weight loss. A detailed inquiry into the abdominal pain and its relationship to eating can be enlightening. Abdominal pain 30 to 60 minutes after eating is common and is often self-treated with food restriction, resulting in weight loss and, in extreme situations, fear of eating, or “food fear.” Postprandial pain may, however, be associated with other intraabdominal processes, including biliary disease, peptic ulcer disease, pancreatitis, diverticular disease, gastric reflux, irritable bowel syndrome, and gastroparesis.

An extensive gastroenterologic workup, possibly including cholecystectomy and upper and lower endoscopy — tests that are often negative in patients with chronic mesenteric ischemia — is generally carried out before the diagnosis is made. An important distinction is that many of these alternative processes do not involve weight loss, whereas it is common in cases of mesenteric ischemia. Since older age and a history of smoking are common in these patients, cancer is often considered, and concern about it may delay the identification of chronic mesenteric ischemia. Nonetheless, in the case of elderly women with a history of weight loss, dietary changes, and systemic vascular disease, chronic mesenteric ischemia must be seriously considered and evaluated appropriately.

**LABORATORY STUDIES**
The laboratory studies that are most useful in potential cases of acute mesenteric ischemia are the assessment of fluid, electrolyte, and acid–base status and evaluation for infection. Many patients present with acidosis due to dehydration and decreased oral intake. However, lactic acidosis often indicates at least segmental, severe ischemia or irreversible bowel injury. It is not helpful to wait for evidence of increasing serum lactate levels to proceed with further testing; ideally, in fact, intervention would occur in patients with acute mesenteric ischemia before lactic acidosis develops, with the goal of saving additional intestine from full-thickness injury. A left shift in the ratio of immature to mature neutrophils or an elevated white-cell count may indicate full-thickness injury to the bowel wall or ischemia with bacterial translocation.

Serum biomarkers have not proved to be as valuable for the early detection of acute mesen-

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**Table 1. Causes of Altered Mesenteric Circulation.**

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<th>Condition</th>
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<tr>
<td>Atherosclerosis</td>
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<td>Arterial embolus</td>
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<td>Arterial dissection</td>
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<td>Thrombosis</td>
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<td>Vasculitis</td>
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<td>Mesenteric venous thrombosis</td>
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<td>Poor cardiac output leading to low mesenteric flow</td>
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<td>Inflammatory or other conditions affecting mesenteric vessels (e.g., pancreatitis, perforated ulcer, tumor)</td>
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teric ischemia as was initially hoped. Despite the many investigations conducted to date, no clinically useful biomarkers have been identified, probably owing to the hepatic metabolism of complex proteins secreted by the intestine.

Tests for markers of nutritional status, such as albumin, transthyretin, transferrin, and C-reactive protein, are the only studies of value in cases of chronic mesenteric ischemia, since they can be used to assess the degree of malnutrition before revascularization is undertaken.

**Diagnostic Imaging**

**Ultrasonography**

In the diagnosis of mesenteric vascular disease, duplex ultrasonography has a high degree of reliability and reproducibility, with both a sensitivity and a specificity of 85 to 90%. It is an effective, low-cost tool that is helpful in the assessment of the proximal visceral vessels, although the results can be limited more distally.

The value of ultrasonographic testing is extremely dependent on the skill of the technologist. In addition, adequate ultrasonographic imaging can be difficult to obtain in patients with obesity, bowel gas, and heavy calcification in the vessels. Adequate ultrasonographic assessment is often impossible in patients with acute mesenteric ischemia because of the length of the study and the abdominal pressure required; it is therefore best reserved for the evaluation of patients with chronic mesenteric ischemia (Fig. 2) and for monitoring after intervention.

**Computed Tomographic and Magnetic Resonance Angiography**

Given its 95 to 100% accuracy, computed tomographic angiography (CTA) has become the recommended method of imaging for the diagnosis of visceral ischemic syndromes (Fig. 1 and 2). Images of the origins and length of the vessels can be obtained rapidly, characterize the extent of stenosis or occlusion and the relationship to branch vessels, and aid in the assessment of options for revascularization.

In addition to providing information about the vasculature, CTA can indicate potential sources of emboli, other intraabdominal structures and pathologic processes, and abnormal findings such as the lack of enhancement or the thickening of the bowel wall and mesenteric stranding associated with diminished blood flow. More ominous pathological findings, including pneumatosis, free intraabdominal air, and portal venous gas, may also be noted.

To determine whether mesenteric ischemia is present, CTA should be performed with the use of intravenous contrast material and reconstruction of images should be achieved with thin axial images (1 to 3 mm). The sensitivity of CTA is not as high for venous thrombosis as it is for arterial disease, but it can be improved with the use of two-phase imaging to enhance visceral venous drainage.

**Magnetic resonance angiography (MRA)** is an attractive option that may provide information about flow and avoid the risks of radiation and use of contrast material that are associated with CTA. However, this test takes longer to perform than CTA, lacks the necessary resolution, and can overestimate the degree of stenosis. Although MRA techniques are evolving, currently CTA imaging is almost always the preferred choice, and the advantages of CTA outweigh any risks associated with the use of this form of imaging among patients with acute mesenteric ischemia.

**Endoscopy**

Endoscopy, which is often part of the investigation of abdominal pain, is most useful in diagnosing conditions other than mesenteric ischemia. These conditions include inflammatory and ischemic changes in the stomach and proximal small bowel, rectum, and right colon. However, endoscopic examination does not reach the majority of sections of the small bowel that are most frequently involved in mesenteric ischemia. This imaging technique is sensitive in identifying late changes, including infarction. However, it lacks sensitivity and specificity in detecting more subtle ischemic changes.

**Catheter Angiography**

Catheter angiography, which was previously considered to be the standard method of diagnosis of mesenteric ischemia, has become a component of initial therapy. Angiography with selective catheterization of mesenteric vessels is now used once a plan for revascularization has been chosen. Single or complementary endovascular therapies, including thrombolysis, angioplasty with or without stenting, and intraarterial vasodilation, are then combined to restore blood flow. Angiography can also be used to confirm
the diagnosis before open abdominal exploration is undertaken.12

INITIAL CARE AND THERAPY

FLUID AND ELECTROLYTE MANAGEMENT

Fluid resuscitation with the use of isotonic crystalloid fluids and blood products as needed is a critical component of initial care. Serial monitoring of electrolyte levels and acid–base status should be performed, and invasive hemodynamic monitoring should be implemented early12; this is especially true in patients with acute mesenteric ischemia, in whom severe metabolic acidosis and hyperkalemia can develop as a result of infarction.8 These conditions may create the potential for rapid decompensation to a systemic inflammatory response or progression to sepsis.

In patients with hemodynamic instability, it is imperative to carefully adjust fluid volume while avoiding fluid overload and to use pressor agents only as a last resort. The fluid-volume requirement can be very high, especially after revascularization, because of the extensive capillary leakage; as much as 10 to 20 liters of crystalloid fluid may be required during the first 24 hours after the intervention.4

EARLY MEDICAL THERAPY

Heparin treatment should be initiated as soon as possible in patients who have acute ischemia or an exacerbation of chronic ischemia. Vasodilators may play a role in care, particularly in combating persistent vasospasm in patients with acute ischemia after revascularization.9 Epithelial permeability increases during acute mesenteric ischemia as high bacterial antigen loads trigger inflammatory pathways,33,34 and the risk of bacterial translocation and sepsis increases.35

Antibiotics can lead to resistance and alterations in bacterial flora; however, their use has been associated with improved outcomes in critically ill patients.36,37 In general, the high risk of infection among patients with acute mesenteric ischemia outweighs the risks of antibiotic use, and therefore broad-spectrum antibiotics should be administered early in the course of treatment.

Oral intake should be avoided in patients with acute mesenteric ischemia, since it can exacerbate intestinal ischemia.38 In patients with chronic mesenteric ischemia, in contrast, enteral nutrition (as long as it does not cause pain) or parenteral nutrition should be considered in order to improve perfusion by means of mucosal vasodilation and to provide nutritional and immunologic benefits.39

TREATMENT OPTIONS

ACUTE MENSERIC ISCHEMIA

Endovascular Repair

Endovascular strategies can theoretically restore perfusion more rapidly than can open repair and may thus prevent progression of mesenteric ischemia to bowel necrosis. Although the use of endovascular techniques is becoming more common, the comparative data on the results with the two approaches in patients with acute mesenteric ischemia are insufficient to show a clear advantage of one approach over the other (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).3,40,41

The largest review of endovascular interventions involved 70 patients with acute mesenteric ischemia. Treatment was considered to be successful in 87% of the patients, and in-hospital mortality was lower among those who underwent endovascular procedures than among those who underwent open surgery (36% vs. 50%). However, patients who presented with more profound visceral ischemia may have been assigned to open revascularization. These and other data40,42 suggest that the use of endovascular procedures for acute mesenteric ischemia is becoming more common; the use of these procedures increased from 12% of cases in 2005 to 30% of cases in 2009.43 These data also show that this strategy may be most appropriate for patients with ischemia that is not severe and those who have severe coexisting conditions that place them at high risk for complications and death associated with open surgery.

An acute occlusion can be treated with a combination of endovascular strategies, with initial treatment aimed at rapidly restoring perfusion to the viscera, most often by means of mechanical thrombectomy or angioplasty and stenting. Thrombolysis is safe and very effective as an adjunct procedure to remove the additional burden of thrombus in patients without peritonitis, and it can be especially helpful in restoring perfusion to occluded arterial branches. These tech-
niques can be effective in treating both embolic and thrombotic occlusions.31,44

Although the use of endovascular therapy for acute mesenteric ischemia precludes direct assessment of bowel viability, 31% of patients who received endovascular therapy in one series were spared laparotomy.31 If endovascular-only therapy is pursued, close monitoring is compulsory, and any evidence of clinical deterioration or peritonitis necessitates operative exploration performed on an emergency basis because 28 to 59% of these patients will ultimately require bowel resection (Table S1 in the Supplementary Appendix).31,42

**Open Repair**
The goals of open surgical therapy for acute mesenteric ischemia are to revascularize the occluded vessel, assess the viability of the bowel, and resect the necrotic bowel.45 Emboli that cause acute occlusion typically lodge within the proximal superior mesenteric artery and have a good response to surgical embolectomy. If embolectomy is unsuccessful, arterial bypass may be performed. This procedure is ideally carried out with autologous grafting, typically of a single vessel distal to the occlusion. However, if distal perfusion remains impaired, local intraarterial doses of thrombolytic agents can be administered.

A hybrid option, retrograde open mesenteric stenting, involves local thromboendarterectomy and angioplasty, followed by retrograde stenting.46,47 This approach reduces the extent of surgery while allowing for direct assessment of the bowel. At this time, however, it is not commonly used, and evidence regarding its outcomes is limited.48

After revascularization, the bowel and other intraabdominal organs are assessed for viability and evidence of ischemia. Frankly ischemic bowel is resected, whereas areas that suggest the possible presence of ischemia may be left for evaluation at a follow-up, or “second-look,” operation. Up to 57% of patients ultimately require further bowel resection,3,42,49 including nearly 40% of patients who undergo a second-look operation.12,49 Short-term mortality after open revascularization ranges from 26 to 65%,3,31,49,50 and rates are higher among patients with renal insufficiency, older age, metabolic acidosis, a longer duration of symptoms, and bowel resection at the time of a second-look operation.49

**CHRONIC MESENTERIC ISCHEMIA**
Revascularization is indicated for all patients with chronic mesenteric ischemia in whom symptoms of this disease develop. Open repair, which was formerly considered to be the standard in such cases, has been surpassed in recent years by endovascular repair, which is now used in 70 to 80% of initial procedures.42 Because angioplasty alone has poor patency and is associated with poor long-term symptom relief,51,52 stenting is used most often (Fig. 2). Open repair can be performed with the use of antegrade inflow (from the supraceliac aorta) or retrograde inflow (from the iliac artery), with either a vein or prosthetic conduit to bypass one or more vessels, depending on the extent of disease. Hybrid procedures involving open access to the superior mesenteric artery and retrograde stenting, as described above, are also options.

Endovascular therapy is a very successful, minimally invasive approach that provides initial relief of symptoms in up to 95% of patients (Table S2 in the Supplementary Appendix) and has a lower rate of serious complications than open repair.52 Despite these advantages, the use of endovascular techniques is associated with lower rates of long-term patency and a shorter time to the return of symptoms.51,53,54 Restenosis occurs in up to 40% of patients, and among these patients, 20 to 50% will require reintervention.55,56 Open repair is associated with slower recovery and longer hospital stays than endovascular repair. Data on mortality are inconsistent; however, patients treated with open repair have improved rates of symptom relief at 5 years and of primary patency (both rates are as high as 92%) and lower rates of reintervention (Table S2 in the Supplementary Appendix).34,57,58,59

Decisions regarding the most appropriate approach to patients with chronic mesenteric ischemia should weigh the morphologic features of the lesion and the patient’s state of health against the short- and long-term risks and benefits of the procedure. In most centers, endovascular therapy is considered to be first-line therapy, particularly in patients with short, focal lesions. The risks associated with future reintervention may outweigh the immediate risks of open surgery among most patients with chronic mesenteric ischemia. In contrast, open repair may be a preferable option for younger, lower-risk patients with a longer life expectancy or for
those whose lesions are not amenable to endo-
vascular techniques.

VENOUS MESENTERIC ISCHEMIA

Unless such treatment is contraindicated, all pa-
tients with venous mesenteric ischemia should
initially receive heparin for systemic anticoagu-
lation, and this treatment should be transitioned
to long-term oral coagulation 24 to 48 hours after
stabilization of the acute condition (see below).
In most cases, anticoagulation is the only therapy
necessary; rates of recurrence and death are lower
among patients who receive anticoagulation than
among those who do not.60 The condition of ap-
proximately 5% of patients who receive conserva-
tive treatment will deteriorate, and further inter-
vention will be required.61 Options for intervention
in patients in whom medical treatment alone is
unsuccessful include transhepatic and percutane-
ous mechanical thrombectomy,62 thrombolysis,30
and open intraarterial thrombolysis.63 The few
studies of the outcomes of these interventions
have shown technical success with low risks of
complications and death,30 although outcomes
may be affected by the selection of patients and
the timing of the intervention.

As in all cases of mesenteric ischemia, any
evidence of peritonitis, stricture, or gastrointes-
tinal bleeding should trigger an exploratory
laparotomy to assess for the possibility of bowel
necrosis and the need for a second-look opera-
tion. The long-term mortality among patients
with venous mesenteric ischemia is heavily in-
fluenced by the underlying cause of thrombosis;
the rate of 30-day survival is 80%, and the rate
of 5-year survival is 70%.61

NONOCCLUSIVE MESENTERIC ISCHEMIA

The outcomes in patients with nonocclusive
mesenteric ischemia depend on the management
of the underlying cause; overall mortality is 50
to 83% among these patients.2 The initial goal of
treatment is to address hemodynamic instability
and in doing so to minimize the use of systemic
vasoconstrictors. Additional treatment may in-
clude systemic anticoagulation and the use of
vasodilators in patients who do not have bowel
infarction. Catheter-directed infusion of vasodi-
latory and antispasmodic agents, most commonly
papaverine hydrochloride, can be used.10 Patients
should be monitored closely by means of serial
abdominal examinations, and open surgical ex-
ploration should be performed if there is con-
cern about the possibility of peritonitis.

FOLLOW-UP

LONG-TERM CARE

The long-term care of patients with mesenteric
ischemia is focused on managing coexisting con-
ditions and risk factors. Therefore, aggressive
smoking-cessation measures, blood-pressure
control, and statin therapy are recommended.
Lifelong preventive treatment with aspirin is
recommended in all patients who undergo endo-
vascular or open repair. Patients who undergo
endovascular repair should also receive clopido-
grel for 1 to 3 months after the procedure. Re-

However, the type of repair performed, in pa-
tients with atrial fibrillation, mesenteric venous
thrombosis, or inherited or acquired thrombo-

Nutritional status and body weight should be
monitored in all patients who have undergone
an intervention for mesenteric ischemia. These
patients may have prolonged ileus and food fear,
and they may require total parenteral nutrition
until full oral intake is possible. In patients who
require bowel resection, diarrhea and malabsorp-
tion may occur. Extensive nutritional support,
lifelong total parenteral nutrition, or even evalu-
ation for small-bowel transplantation may be
required in patients with persistent short-gut
syndrome.

ASSESSMENT

Because the recurrence of symptoms is common
in patients with a history of mesenteric ischemia,
life-long repeated assessment of vascular
patency is indicated. Duplex ultrasonography
should be performed every 6 months for the first
year after repair, then yearly thereafter. All pa-
tients should be informed about the risks and
warning signs of stenosis, occlusion, and re-
peated episodes of ischemia.

Any recurrence of symptoms should prompt
diagnostic imaging. Given the high morbidity
and mortality associated with acute mesenteric
ischemia, preemptive revascularization is advised
if evidence of recurrent stenosis or occlusion is
identified.
REFERENCES

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