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STATE OF THE ART REVIEW

Secondary peritonitis: principles of diagnosis and intervention

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ABSTRACT

Secondary peritonitis accounts for 1% of urgent or emergent hospital admissions and is the second leading cause of sepsis in patients in intensive care units globally. Overall mortality is 6%, but mortality rises to 35% in patients who develop severe sepsis. Despite the dramatic growth in the availability and use of imaging and laboratory tests, the rapid diagnosis and early management of peritonitis remains a challenge for physicians in emergency medicine, surgery, and critical care. In this article, we review the pathophysiology of peritonitis and its potential progression to sepsis, discuss the utility and limitations of the physical examination and laboratory and radiographic tests, and present a paradigm for the management of secondary peritonitis.

Introduction

Inflammation of the peritoneum—peritonitis—is divided into primary and secondary peritonitis. Primary peritonitis results from bacterial translocation, hematogenous spread, or the iatrogenic contamination of the abdomen without a macroscopic defect in the gastrointestinal tract. By contrast, secondary peritonitis results from the direct contamination of the peritoneum by spillage from the gastrointestinal or urogenital tracts or their associated solid organs. Tertiary peritonitis refers to secondary peritonitis that persists for more than 48 hours after an attempt at surgical source control.[1-3]

The principles of surgical management of secondary peritonitis have changed little since the 1900s: eliminate the septic focus, remove necrotic tissue, and drain purulent material.[2] The timing and selection of patients for surgery, however, has shifted substantially with the advent of modern critical care, broad spectrum antibiotics, minimally invasive interventions, and diagnostic tools. In current practice, patients with generalized peritonitis (rigidity, rebound tenderness, or guarding in all four abdominal quadrants) or sepsis need rapid resuscitation and urgent surgical exploration, and patients with localized peritonitis (peritoneal signs limited to one or two abdominal quadrants) and laboratory and imaging findings consistent with a contained process may undergo more limited drainage or a trial of non-surgical management. The much larger proportion of patients who present with acute abdominal pain without clear peritonitis are typically subjected to a broad array of laboratory and imaging tests in an effort to establish a definitive diagnosis.

Laboratory and imaging tests have revolutionized the diagnosis of intra-abdominal pathologies, but their use has the potential to delay diagnosis, increase cost, and expose patients to ionizing radiation. More importantly, the apparently objective data from these tests may be given inappropriate weight in clinical decision making.[4-6] The judicious use of imaging, laboratory tests, and physical examination are critical to the rapid evaluation and triage of patients with acute abdominal pain or peritonitis.

This review discusses the pathophysiology of peritonitis and its potential progression to sepsis, considers the utility and limitations of the physical examination and laboratory and radiographic tests, and presents a paradigm for the management of secondary peritonitis.

Sources and selection criteria

We identified references through searches of publications listed by PubMed from January 2000 to August 2017. We used the search terms "peritonitis", "secondary peritonitis", "abdominal sepsis", "mesenteric ischemia", "perforated viscus", "bowel obstruction", "intra-abdominal abscess", and "acute abdominal pain". We also identified references from the selected manuscripts and from relevant review articles. We reviewed human, animal, and in vitro studies published in English. We prioritized high quality, large, prospective randomized controlled trials (RCTs) performed in the past 10 years, although we included meta-analyses, systematic reviews, and observational studies whenever RCTs were unavailable. We did not include case reports or case series.

Epidemiology

Secondary peritonitis is a common clinical problem that affects a wide range of patients. In a retrospective observational study of patients admitted urgently or emergently to 81 hospitals in Washington State between 1997 and 2000, 11 200 patients had a diagnosis of secondary peritonitis, with an overall rate of 9.3 per 1000 admissions.[7] Approximately 11% of patients with peritonitis in this cohort developed severe sepsis, with single organ failure in 74% of patients and multi-organ failure in 20%. The overall mortality in patients with peritonitis was 6%, but mortality rose to 34% for patients with severe sepsis. Patients with peritonitis

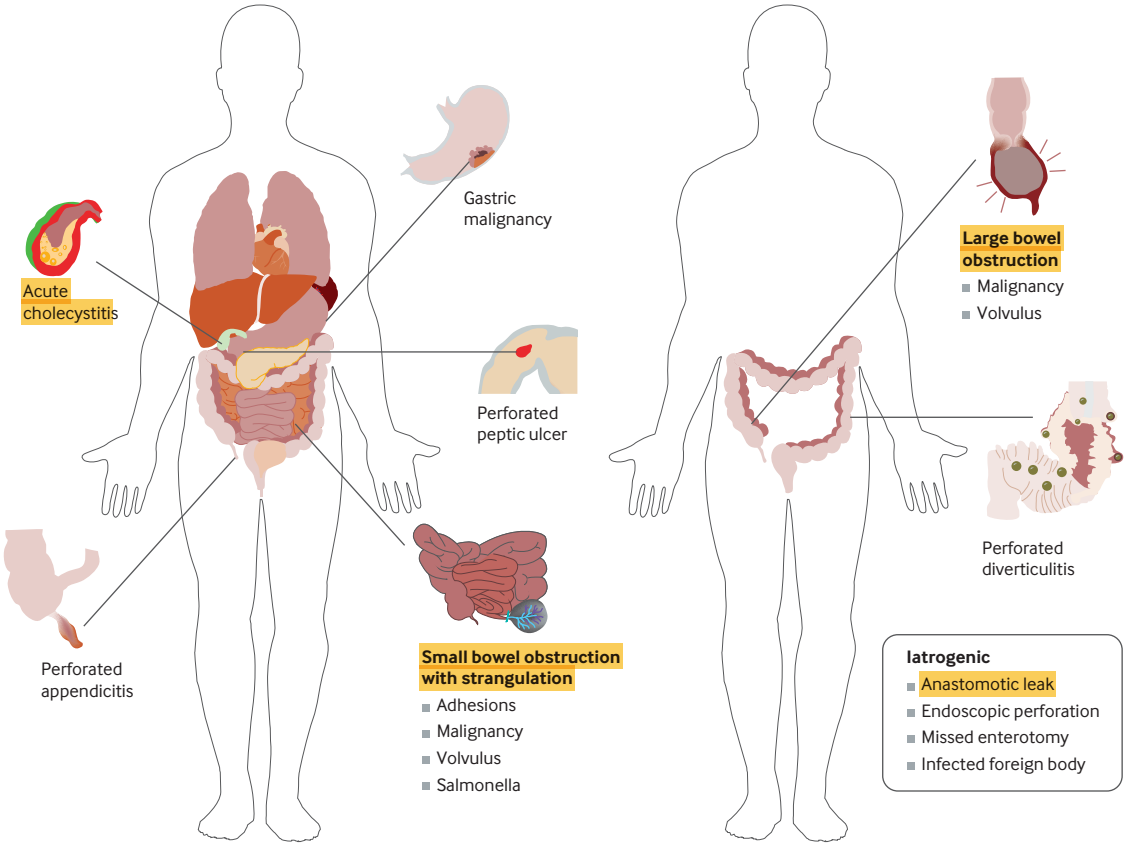

Fig 1 | Common etiologies of secondary peritonitis in adults

who developed severe sepsis were older (68 (SD 19) *v* 46 (25) years; P<0.001) and more likely to have pre-morbid organ dysfunction. These findings are broadly consistent with a large observational study of patients who needed surgery for secondary peritonitis at a representative sample of 66 French hospitals between January and June 2005.[8] At presentation, 26% of the 841 patients had at least one comorbidity and 25% had failure of at least one organ.

Table 1 | Source and severity of secondary peritonitis

Severity	Source					
	Stomach/ duodenum	Biliary tract	Small bowel	Appendix	Colon	Unspecified*
Proportion (%)	8-18	1-6	7-13	31-50	15-32	24
Localized peritonitis or abscess (%)	72	74	55	99	75	90
Generalized peritonitis (%)	29	26	44	1	25	10
Mean age (years)	60	68	62	39	67	-
Diabetes (%)	7	10	4	2	3	-
Malignancy (%)	7	4	10	2	17	-
Mechanical ventilation (%)	66	64	77	46	76	-
Vasopressors (%)	61	41	57	39	68	-
Hemodialysis (%)	16	18	12	4	13	-
Death (%)	17	14	27	2	23	-

Adapted from Anaya et al,[7] Gauzit et al,[8] and Sartelli et al.[9] In addition to non-postoperative patients, Anaya et al included postoperative patients admitted urgently or emergently with secondary peritonitis, thus excluding postoperative patients with iatrogenic perforation or anastomotic leak that was recognized before discharge.[9] The authors also included patients with peritonitis who were found to have mesenteric ischemia or volvulus, shown together as "Unspecified." Gauzit et al specifically excluded postoperative patients as well as patients with acute appendicitis, cholecystitis, or diverticulitis without peritonitis.[7] Sartelli et al included both postoperative and non-postoperative patients with intra-abdominal infection.[9]
*Unspecified sources occurred in patients with mesenteric infarction (73%) or volvulus (35%) in whom a single site of perforation was not identified.[7]

In a third large observational study of complicated intra-abdominal infections from 68 European hospitals, the findings emphasized the importance of postoperative intra-abdominal infections.[9] Of 2152 patients enrolled, 1701 (79%) were classified as having community acquired abdominal infections, and 451 (21%) were classified as having nosocomial infections. Most (82%) nosocomial infections occurred in postoperative patients, and more than 99% of these were the result of anastomotic leak. Of these, 40% resulted from colorectal leaks, 32% from gastroduodenal leaks, 15% from biliary leaks, 11% from pancreatic leaks, and 2% from urinary leaks. Figure 1 and table 1 summarize the etiology, pre-morbid risk factors, and rates of organ failure for patients in these three studies. Notably, whereas appendicitis is the most common source of secondary peritonitis, it typically occurs in younger patients with fewer comorbidities and is associated with lower morbidity and mortality.

Mortality in secondary peritonitis depends in part on patients' age; pre-existing cardiovascular, liver, renal, or neurologic disease; a non-appendicular source of infection; delay in intervention beyond 24 hours; and the extent of peritonitis.[7 9-11] The optimal timing of intervention is discussed in the management section below. The importance of the extent of peritonitis is highlighted in a prospective study of 92 patients with secondary peritonitis proven on laparotomy.[12] Patients with four quadrant peritonitis at the time of surgery had a mortality rate of 36% compared with an average in-hospital mortality of 19% in all patients (P=0.003).[12] The presence of fecal peritonitis was also a

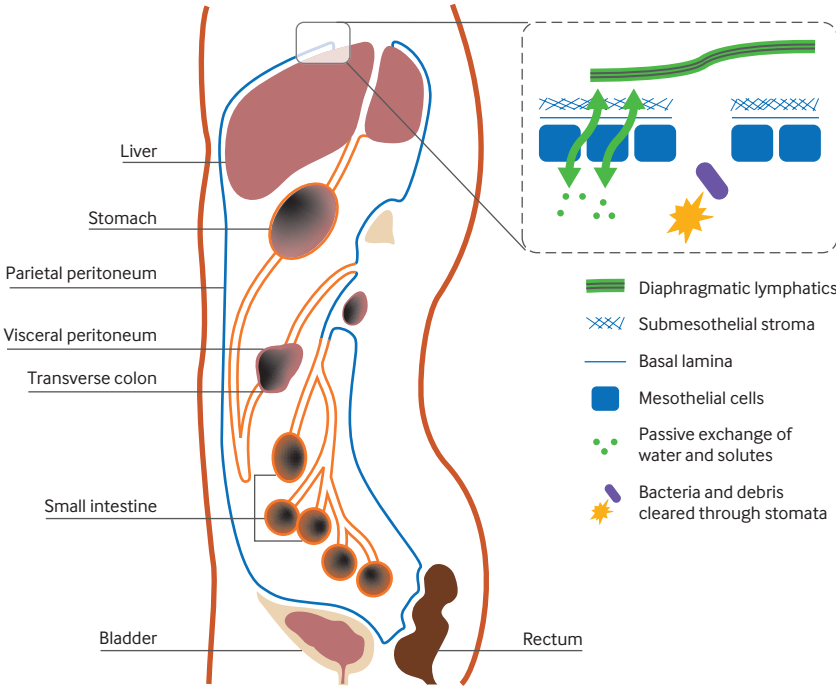

Fig 2| Peritoneum and diaphragmatic lymphatic drainage. The abdominal cavity is divided by the mesentery into two major compartments, the greater and lesser sacs. The lesser sac is bound by the retroperitoneum posteriorly, the stomach and greater omentum anteriorly, and the transverse colon and transverse colon mesentery inferiorly. The remainder of the abdominal cavity is the greater sac, and the two are connected via the foramen of Winslow. This is relevant to the clinical diagnosis of secondary peritonitis as perforation into the lesser sac, such as a perforated ulcer in the posterior gastric wall, may be temporarily contained in the lesser sac, preventing the patient from developing peritonitis. The peritoneum forms a semipermeable barrier through which water and solutes are passively exchanged. Regular circulation of peritoneal fluid is driven in part by the movement of the diaphragm.[14 15] Bacteria and larger debris are cleared via stomata, lymphatic portals between mesothelial cells, which are concentrated on the diaphragmatic surface.[16] The embryology, histology, and physiology of the peritoneum were reviewed recently by van Baal et al[13]

very poor prognostic factor, with an in-hospital mortality of 38% compared with an average of 19% for the entire group. These investigators also found that in-hospital mortality was significantly higher in patients with diabetes (mortality 50% compared with average 19%; P=0.009).

Pathophysiology

The peritoneum is formed from a monolayer of mesothelial cells that coats the abdominal wall (parietal peritoneum) and abdominal viscera (visceral peritoneum). This monolayer, with its basal lamina and submesothelial stroma, creates a semipermeable barrier through which water and solutes are passively exchanged.[2 13] Larger particles and bacteria are cleared through stomata, lymphatic channels between mesothelial cells, which are concentrated on the diaphragmatic surface (fig 2).[16] The rapid removal of intra-abdominal microbes via these lymphatics is central to the pathophysiology of abdominal infections, as uncontained contamination can lead to rapid bacteremia and sepsis.[2 13 16]

Whereas primary peritonitis is usually a monomicrobial aerobic infection, secondary peritonitis is usually polymicrobial. The microbiology of secondary peritonitis is influenced by the site of perforation and by host factors, including whether the perforation is "community acquired" or has occurred in a postoperative patient. The microbiology of secondary peritonitis, including the emergence of resistant organisms, has been investigated in several recent studies.[9 17-19]

Bacteria spilled into the peritoneum are recognized directly by pattern recognition receptors of the innate immune system and indirectly via molecules released from injured mesothelial cells.[20] The initial stage of the response depends on an influx of macrophages and the production of pro-inflammatory cytokines including tumor necrosis factor α, interleukin 1, and interleukin 6. Neutrophils arrive within two to four hours and are the predominant cell type in the peritoneum from 48 to 72 hours. Bacterial destruction releases lipopolysaccharide and other cellular components that further stimulate the host pro-inflammatory response. Experimental evidence indicates that a robust local inflammatory response is needed to control peritonitis; however, if the local inflammatory response spreads to the systemic circulation, it can produce sepsis and increase mortality.[21-27] The pathophysiology of sepsis and organ injury has been recently reviewed by Gotts and Matthay in the *BMJ*.[28]

Recent experimental work has highlighted the many important roles of eicosanoid products of arachidonic acid as both mediators and effectors in the programmed transition from a pro-inflammatory to an anti-inflammatory state.[29] Pro-inflammatory lipid mediators such as leukotriene B4 and the prostaglandins PGE_2 and PGI_2 act in concert with pro-inflammatory cytokines and complement components C3a and C5a to promote leukocyte chemotaxis. A complex and less well understood interaction between infiltrating leukocytes and resident cells of the inflamed tissue promotes the production of four other classes of lipid mediators: lipoxins, resolvins, protectins, and maresins. These pro-resolving lipids have broad functions in promoting resolution of inflammation, including reducing local vascular permeability, stimulating the clearance of apoptotic neutrophils, and stimulating caspase dependent granulocyte apoptosis.[30] The role of lipid derived inflammatory mediators was reviewed recently by Serhan.[29]

One group of investigators advanced the hypothesis that peritonitis is a combined infectious and inflammatory process and that despite clearance of the peritoneum of infection with surgery and antibiotics, the overall morbidity and mortality of peritonitis is related in large part to systemic inflammation and organ injury.[31] Limiting the systemic inflammatory response from secondary peritonitis depends on the host's ability to contain the source of contamination. Activation of the coagulation cascade leads to the local production of fibrin, potentially walling off the area of contamination to facilitate abscess formation. The greater omentum plays a critical role, both as a route of rapid neutrophil deployment and as a physical barrier that contributes to confinement of the infection.[32-34] If this is successful, the source of contamination is contained, preventing further clearance of bacteria and inflammatory cytokines into the bloodstream.[35]

These experimental data inform current surgical management of peritonitis. In patients with a perforated viscus, the degree to which the patient is able to contain the contamination is critical. Patients with uncontrolled contami-

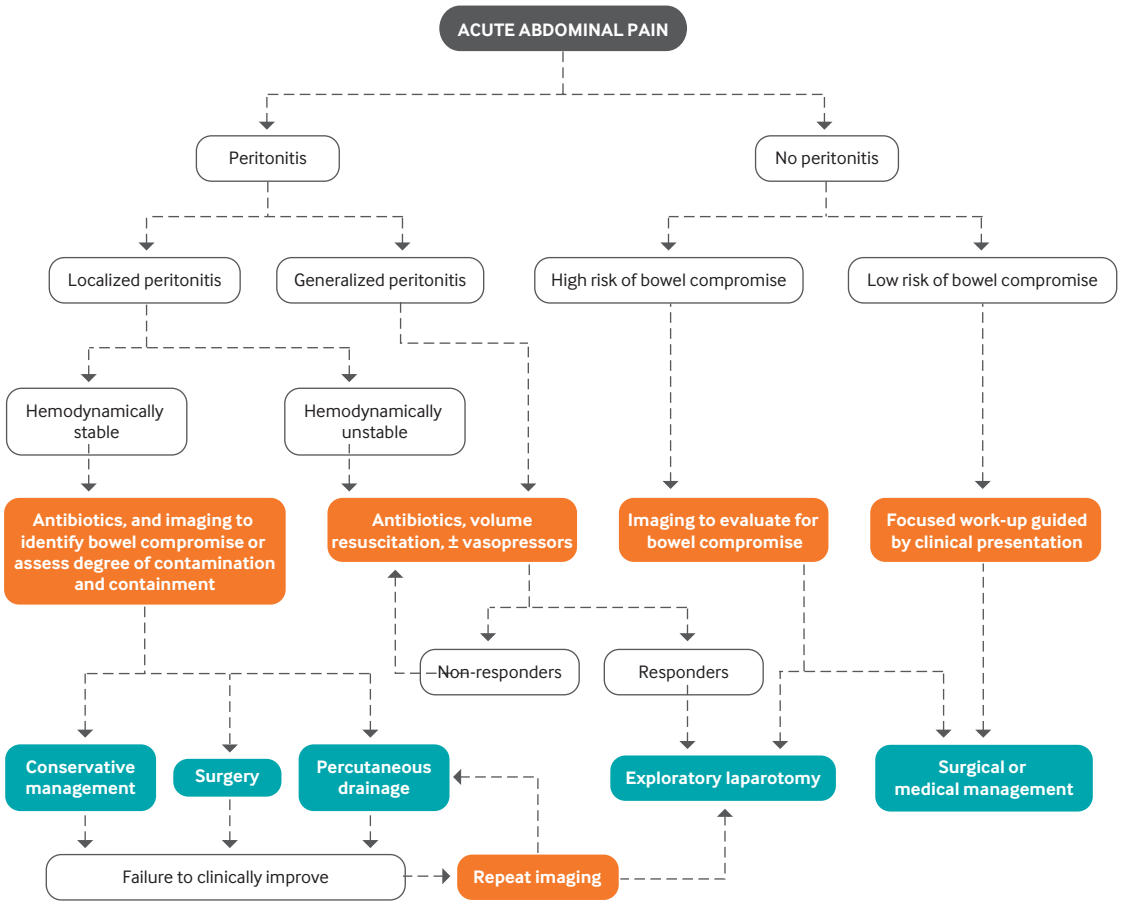

Fig 3| Management algorithm. Patients with localized peritonitis who are hemodynamically stable should receive broad spectrum antibiotics and cross sectional imaging.[5 41-43] Those with evidence of bowel compromise, feculent, or four quadrant contamination should have laparotomy.[19 44] Patients with acute appendicitis, acute cholecystitis, or perforated peptic ulcer may undergo laparoscopic resection or repair. Select patients with purulent peritonitis or in whom the diagnosis is unclear may undergo laparoscopy with lavage or conversion to laparotomy as necessary.[45-48] Those with contained perforation should be managed with a trial of conservative management or percutaneous drainage depending on the accessibility and size of the abscess.[49-51] Failure to improve clinically with conservative management or after intervention should prompt repeat imaging with percutaneous drainage or exploration as needed. Patients with generalized peritonitis or localized peritonitis with hemodynamic instability should receive fluid resuscitation and broad spectrum antibiotics, with vasopressors if necessary.[28] Once patients have been resuscitated, they should be taken for urgent laparotomy. We advise that the rare patient with abdominal sepsis who cannot be stabilized with appropriate fluids, antibiotics, and vasopressors should not be taken for surgery because of the negligible chance of survival. In some cases, these patients may be candidates for bedside procedures. Patients without peritonitis should be evaluated for clinical risk of bowel compromise. Patients over 65 years, or with significant cardiovascular disease or bowel obstruction, should be considered to be at high risk of bowel compromise and should receive cross sectional imaging (see "Identification of patients at high risk of bowel compromise").[52-54] Patients without peritonitis or high risk of bowel compromise should undergo focused investigation guided by the clinical presentation (see "Imaging to clarify diagnosis"). The management of these patients is beyond the scope of this review. This algorithm deliberately excludes hemodynamically unstable patients with abdominal pain but without peritonitis. This combination of symptoms covers a broad range of diagnoses that are beyond the scope of this review

nation, or those with ongoing sepsis and a clear abdominal source, need urgent source control. Similarly, every effort must be made to minimize contamination of the peritoneum by intervening early in patients who have evidence of impending bowel compromise.

Clinical presentation

Despite a common embryologic origin, the innervation of the parietal and visceral peritoneum is distinct and dictates the symptoms that patients experience following injury and inflammation involving the respective peritoneal surfaces. The parietal peritoneum is innervated by the phrenic, thoraco-abdominal, subcostal, and lumbosacral nerves in the upper abdomen and by the obturator nerve in the pelvis.[13] These nerves contain motor, sensory, and sympathetic nerve fibers. By contrast, innervation to the visceral peritoneum is less well understood but may occur through the splanchnic nerves and by the celiac and mesenteric plexus.[36] As a result, the parietal peritoneum is sensitive to pressure, temperature, and laceration, whereas the visceral peritoneum is sensitive only to chemical irritation and distension.[13] The genitourinary organs and pancreas share the visceral afferent innervation with the visceral peritoneum, and inflammation of these organs can present with similar symptoms to inflammation of the intra-abdominal viscera.

Parietal peritonitis manifests as sharp, constant, local-

Table 2 | Utility of serum biomarkers in predicting intestinal compromise

Biomarker	Sensitivity (%)	Specificity (%)
Base deficit[52 65]	75*; 72-80†	80*; 38-50†
White blood cell count[52 53 65-67]	45-81*; 80-82†	37-74*; 40-58†
L-lactate[66 68-70]	78-100	36-53
D-lactate‡[71-73]	82	77
D-dimer§[74-79]	89-96†	40†
Procalcitonin[80-85]	72*	73*

*Predicts strangulated bowel.
†Predicts acute mesenteric ischemia.
‡Product of bacterial fermentation; serum concentrations are typically low but have been reported to rise in mesenteric ischemia owing to increased intestinal permeability.[73]
§Byproduct of plasmin mediated breakdown of cross linked fibrin, and therefore a sensitive test of thrombus formation.

ized pain. If the affected portion of peritoneum is next to a superficial muscle group, peritonitis may be associated with rigidity of that abdominal wall musculature and guarding. Patients typically lie still.[2] By contrast, visceral peritonitis produces a characteristic "colicky" pain, which is paroxysmal in nature and is referred to a portion of the midline anterior abdomen corresponding to the cell bodies of the associated afferent nerves. Patients typically writhe in pain. Visceral inflammation can cause symptoms associated with parietal peritonitis when the visceral process is transmural and the involved viscera are close enough to a parietal peritoneal surface to cause secondary inflammation.

Several clinical scoring systems have been created to predict the prognosis of secondary peritonitis according to the cause. To date, however, surgical disease specific scores have not been demonstrably superior to general disease severity scores such as the acute physiology and chronic health evaluation (APACHE) II or III, or the sequential organ failure assessment (SOFA), so these scores are not routinely used to direct clinical care.[11 37-40]

Initial examination

The initial evaluation of a patient with acute abdominal pain should be rapid and focused. The primary goal of the examiner is to assess the clinical severity of the patient's condition and to rapidly triage the patient to resuscitation and immediate surgery versus imaging with limited intervention or a trial of conservative management (fig 3). The secondary goal is to identify patients who do not have outward signs of peritonitis but who nonetheless need urgent surgery owing to bowel compromise.

After observing the patient's overall appearance and vital signs, the examiner should determine the timing, location, and character of the patient's pain, along with associated symptoms. It is important to determine whether the patient has had similar symptoms in the past. The examination should focus on identifying generalized peritonitis (rigidity, rebound tenderness, or guarding in all four abdominal quadrants) or localized peritonitis (peritoneal signs limited to one or two abdominal quadrants). Of note, abdominal auscultation has no role in the evaluation of acute abdominal pain.[55-58] Although some physicians question the reliability of the physical examination after patients have received narcotics, three small RCTs have shown that early pain relief does not alter the diagnostic accuracy of the physical examination or operative decision making.[59-61]

Particular care is needed when examining older or obese patients, as the physical examination may be unreliable.[62-64] The identification of patients with a small bowel obstruction who have strangulated bowel and the identification of patients with mesenteric ischemia require a high index of suspicion, as the clinical presentation and examination have low sensitivity.[52]

Laboratory measures

Laboratory testing has a well established role in the diagnosis of a wide range of acute abdominal pathologies, including pancreatitis, cholecystitis, and acute appendicitis. However, the role of laboratory tests in the initial management of secondary peritonitis is limited (fig 3). Similarly, laboratory testing has a limited role in the identification of patients with intestinal compromise who are at high risk of perforation. Here we will review the available studies on the role of widely available laboratory tests in the management of secondary peritonitis. As most studies have focused on the laboratory identification of intestinal compromise, these findings are directly compared in table 2.

White blood cell count

Elevation of the white blood cell count (WBC) in peripheral blood is a common sign of bacterial infection and may be accompanied by an increase in the relative proportion of mono-lobed and bi-lobed leukocytes, in a so-called "left shift."[86] However, leukocytosis is a non-specific response to physiologic stress and is known to occur after intense exercise, in periods of psychological stress, and in pregnancy.[87] Perhaps because of this poor specificity, WBC has not been rigorously evaluated in the diagnosis of secondary peritonitis or as a predictor of the need for immediate surgery in secondary peritonitis.[41] Although many authors have studied the utility of WBC in diagnosis of specific intra-abdominal pathologies, most findings have been disappointing. For example, in a meta-analysis of 23 studies of patients with clinical suspicion for acute appendicitis, the pooled sensitivity of leukocytosis for the diagnosis of acute appendicitis was 0.79 (95% confidence interval 0.78 to 0.81) and pooled specificity was 0.55 (0.54 to 0.57).[88] In a recent systematic review including five studies on the diagnostic value of WBC in acute diverticulitis, WBC could not be reliably used to predict the severity of acute diverticulitis or the need for surgery.[89] Similarly, available data suggest that leukocytosis is not sufficiently specific to be used to differentiate bowel strangulation or mesenteric ischemia from other causes of acute abdominal pain.[52 53 65 66 74 90 91] Thus, leukocytosis alone does not have a role in the routine diagnosis of secondary peritonitis or in the identification of patients at risk of bowel compromise.

Lactate

L-lactate is produced as a byproduct of glycolysis in all human cells. In hypoxic conditions, excess L-lactate is produced and released into the venous system.[92] Importantly, L-lactate produced in the bowel drains through the portal circulation into the liver, which is capable of clearing large quantities of lactate via gluconeogenesis and the Cori cycle.[93 94] Lactate has been studied extensively as a marker of systemic hypoperfusion and is independently associated

TEST	SENSITIVITY (%)	SPECIFICITY (%)	IONIZING RADIATION (mSv)	STRENGTHS	LIMITATIONS	REFS
Examination and laboratory tests	73-88	41	0		▪ Examination limited by body habitus and mental status	4, 113, 114
Plain film radiography	30-88*	43*-87	0.01-0.25†	▪ Rapid ▪ Inexpensive ▪ Sensitive in detection of foreign body	▪ Limited by body habitus ▪ Low sensitivity for bowel strangulation or ischemia	4, 106, 114, 144, 145
Ultrasonography	70‡	85‡	0	▪ Directly augments physical examination ▪ Pregnancy related and pelvic pathology ▪ Isolated right upper quadrant pain	▪ Operator dependent ▪ Limited by body habitus and abdominal gas	4, 146-152
Computed tomography	78-96	77-95	10	▪ Rapid ▪ Widely available ▪ Familiar to clinicians ▪ Operator independent	▪ Ionizing radiation§ ▪ Iodinated contrast for best results	4, 5, 106, 113, 114, 145, 153
Magnetic resonance imaging	-	-	0	▪ No ionizing radiation ▪ No contrast needed ▪ Operator independent ▪ Comparable to computed tomography in diagnosis of acute colonic diverticulitis	▪ Slower than computed tomography ▪ Less familiar to clinicians ▪ More expensive ▪ Motion degradation ▪ Limited access ▪ Incompatible with older surgical implants	148, 154-156

Fig 4| Utility of radiographic studies in diagnosis of acute abdominal pain. *When used in addition to physical examination and laboratory tests; if used in addition to computed tomography, improves specificity (87% *v* 41%) but not sensitivity (88% in both groups).[4] †Organ dose ranges from 0.01 mSv to lung in anterior-posterior chest film to 0.25 mSv to stomach in anterior-posterior film of abdomen.[106] ‡When used in addition to physical examination and laboratory tests. §Assuming induction of cancer is proportional to radiation dose even for very small doses of radiation, so-called linear non-threshold model, risk of death from cancer attributable to single computed tomography scan is approximately 0.02% in 50 year old patient and 0.06% in 25 year old patient[106]

with mortality in surgical patients with sepsis.[95 96] However, it has not been rigorously evaluated as a marker for diagnosis in secondary peritonitis or to triage patients to surgery. Several small studies have evaluated the utility of serum lactate in patients who present with an acute abdomen and a clinical suspicion of mesenteric ischemia (table 2).[97] In these small and highly selected populations, the authors report a sensitivity of 78-100% but specificity of only 36-53%.[66 68-70] In conclusion, L-lactate is a non-specific marker of systemic hypoperfusion. We recommend the use of serum L-lactate to guide initial resuscitation and as a marker of global illness, but not as a marker of intestinal ischemia.

Metabolic acidosis

Metabolic acidosis is often expressed as base deficit—the amount of base that must be added to return 1 L of whole blood to a normal pH. Base deficit is considered superior to pH or bicarbonate in measurement of metabolic acidosis because it is not subject to the compensatory mechanisms that act to maintain a normal pH.[98] However, although measures of metabolic acidosis, including base deficit, are reliable predictors of severity of injury and mortality in trauma, and have been widely studied endpoints in resuscitation,[98] their utility in identifying patients with secondary peritonitis or guiding surgical management is unclear. To the best of our knowledge, metabolic acidosis has not been rigorously evaluated in the diagnosis of secondary peritonitis or in identifying patients who need urgent surgery. Several small studies have assessed the utility of metabolic acidosis in identifying patients with strangulated obstruction or mesenteric ischemia (table 2),[52 53 65 66 80] and they suggest that metabolic acidosis is not a reliable predictor of either diagnosis.

Other tests

Procalcitonin may have some value in distinguishing bacterial infections from other sources of inflammation,[80-83 99] but the data are not sufficient to recommend the routine use of procalcitonin in the diagnosis of secondary peritonitis or in the identification of patients with bowel compromise. Similarly, C reactive protein may have a role in predicting the need for surgery in patients with abdominal pain,[100 101] or in identifying post-operative patients who develop a septic complication,[102-105] but the data are insufficient to recommend routine clinical use.

Table 3 | Hinchey classification of perforated diverticulitis

Hinchey class	Description
I	Peri-colonic abscess
II	Pelvic or intra-abdominal abscess
III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis

Adapted from Hinchey et al.[108]

Imaging

Patients who present with abdominal pain often receive extensive imaging, including computed tomography, ultrasonography, and radiography, as well as laboratory testing. However, imaging studies should be chosen judiciously to avoid delaying definitive management, moving the acutely ill patient out of the resuscitation room, exposing the patient to ionizing radiation, and introducing potentially spurious data to the decision making process. Here we discuss the role of imaging in the investigation of patients with acute abdominal pain and review the diagnostic value of specific radiographic findings. Figure 4 summarizes the relative strengths and weaknesses of commonly available imaging modalities.

Patients with generalized peritonitis or localized peritonitis with hemodynamic instability do not need imaging, as this would not alter the need for laparotomy (fig 3). One important exception is the hemodynamically stable patient with peritonitis and high suspicion for acute mesenteric ischemia. In this case, preoperative computed tomography angiography may guide rapid vascular intervention, which should be accompanied by laparotomy.[44]

Imaging to confirm contained perforation

In a hemodynamically stable patient with localized peritonitis, imaging is important to assess the extent of initial contamination and the degree to which the contamination has been contained. A contained perforation without widespread contamination of the abdomen may be managed with antibiotics alone, augmented by percutaneous drainage of safely accessible abscesses larger than 3-4 cm (fig 3).[49-51]

Determining the class of perforated diverticulitis is a good example of this challenge. In a retrospective review of 75 patients who presented with perforated diverticulitis and who underwent computed tomography followed by surgery, 64% of patients were correctly staged by computed tomography.[107] The specificity of computed tomography for each Hinchey class (described in table 3) was high (83-95%). The same was true for sensitivities (76-100%), with the exception of the sensitivity of computed tomography for Hinchey III diverticulitis (42%). As a result, patients with purulent peritonitis were commonly misclassified as having colonic or pelvic abscesses. This is particularly relevant now, as multiple investigators seek to understand the appropriate role of laparoscopic lavage in Hinchey III diverticulitis.[109-111]

Perforated appendicitis and gastroduodenal ulcer are two other situations in which an assessment of the degree of containment may guide the management of clinically stable patients. However, no data are available on the reliability of imaging in these tasks.

In summary, limited data are available to validate the use of any imaging technique in assessing the containment of visceral perforation. The available data in perforated diverticulitis expose a particular weakness in the sensitivity of computed tomography for the detection of purulent peritonitis.

Imaging to clarify diagnosis

The most challenging subset of patients who present with acute abdominal pain are those without obvious peritonitis. Abdominal pain is the leading cause of visits to American emergency departments among patients aged 18-64 years, accounting for 10 million (8% of all visits) in 2012.[112] As a result, many investigators have attempted to determine the most effective use of available imaging modalities to identify the small subset of these patients with urgent surgical needs and triage the remainder for admission or discharge.

A recent multicenter prospective study evaluated the utility of various imaging methods in a series of 1021 patients presenting with non-traumatic acute abdominal pain to six academic medical centers in the Netherlands.[4] Each patient had a full history, physical examination, and laboratory testing, and a preliminary diagnosis was recorded. Patients who were thought to need imaging then had plain radiographs of the chest and abdomen, abdominal ultrasonography, and computed tomography of the abdomen and pelvis. Each study was reviewed independently by a radiologist with access to all of the clinical data but not the other imaging. Final diagnosis was determined by review of medical records at six month follow-up. The authors used these data to compare a variety of imaging strategies including the use of physical examination and laboratory findings alone or with any single imaging modality and the conditional use of ultrasound or computed tomography based on patient demographics, the location of pain, or results of other imaging studies.

On final review, 671 patients were admitted to the hospital, 661 (65%) patients had "urgent" diagnoses and 483 (48%) patients needed surgery at that admission. Clinical diagnosis with or without plain radiographs was relatively sensitive for urgent conditions (88%, 95% confidence interval 86% to 91%) but had limited specificity (41%, 36% to 46%, clinical examination alone; 43%, 38% to 48%, clinical examination with plain films). Ultrasound alone or computed tomography alone in all patients had no effect on sensitivity but significantly improved specificity (77%, 72% to 81%, for computed tomography in all; 85%, 81% to 88%, for ultrasound in all; 41%, 36% to 46%, for clinical examination alone). The only imaging strategy more sensitive than clinical examination alone was a conditional strategy in which all patients underwent abdominal ultrasound, and computed tomography was performed if the ultrasound was normal (sensitivity 94%, 92% to 96% *v* 88%, 86% to 91%). This was a relatively sick population, and as a result the sensitivity of the clinical examination may have been overestimated. However, the results emphasize the importance of trusting a concerning physical examination and using additional imaging only when truly necessary to clarify the diagnosis.

Three small, randomized trials have attempted to assess the value of routine abdominopelvic computed tomography imaging in patients with acute abdominal pain. Ng et al randomized 120 patients who presented to a single teaching hospital in England with acute abdominal pain to "standard practice" or to receive computed tomography

of the abdomen/pelvis within 24 hours of presentation.[113] Standard practice involved plain radiographs, with additional computed tomography, ultrasound, or fluoroscopy at the discretion of the clinical team. Compared with diagnoses assessed at six months, 50% of pre-imaging diagnoses were correct. This improved to 75% in the standard practice group and 78% in the early computed tomography group. The major difference was that more "serious" diagnoses were missed in the standard practice arm than in the early computed tomography arm (18% *v* 5%; P=0.04). This approach may have contributed to a higher mortality in the standard practice group (7% *v* 0%). A similar trial randomized 205 patients to standard practice (supine abdominal and upright chest radiographs on presentation with computed tomography if deemed clinically indicated) or to computed tomography scan within one hour.[114] The leading diagnosis as well as the clinical certainty was recorded at randomization, at 24 hours, and at six months. Half of patients in the standard practice group ultimately underwent computed tomography on the basis of perceived clinical need. Diagnostic certainty improved significantly more in the early computed tomography arm compared with the standard practice arm (36% correct diagnoses at randomization compared with 84% at 24 hours in the early computed tomography group, compared with 49% correct diagnoses at randomization and 73% at 24 hours; P<0.001). However, despite the increase in diagnostic certainty at 24 hours, no differences were seen in the need for admission, length of hospital stay, or six month mortality. Another study randomized 203 patients with acute abdominal pain to routine computed tomography or selective computed tomography of the abdomen/pelvis.[5] The confidence to treat patients operatively increased significantly in the routine computed tomography group, but no difference existed between the two groups in diagnostic accuracy, the need for admission, need for exploratory laparotomy, length of stay, or mortality.[5]

These data suggest that imaging, particularly computed tomography, has an important role in patients without peritonitis to improve diagnostic certainty. Although imaging did not improve the diagnostic sensitivity in most of the available studies, one of the studies reported a significant improvement in the early diagnosis of serious conditions,[113] which seemed to be associated with decreased mortality. This finding highlights the importance of maintaining vigilance regarding the possibility of occult bowel compromise in patients with an equivocal physical examination.

Identification of patients at high risk of bowel compromise

Among the large population of patients who present with abdominal pain, an important subset seem clinically well but need urgent surgery owing to intestinal ischemia. The two most common causes are bowel obstruction with strangulation and mesenteric ischemia. Although prominent historical studies have highlighted the challenge of predicting intestinal strangulation in small bowel obstruction,[52 54] a recent retrospective review highlighted the relative value of computed tomography imaging. The investigators retrospectively reviewed 192 patients who were admitted with small bowel obstruction and underwent exploratory laparotomy.[53] They compared preoperative clinical, laboratory, and imaging data on patients who were or were not ultimately found to have strangulated bowel that needed resection. On computed tomography, patients with strangulated small bowel were significantly more likely to have ascites, thick walled small bowel, segmental mesenteric fluid, fat stranding, reduced bowel wall enhancement, and evidence of closed loop bowel obstruction. After multivariate analysis, the significant predictors of bowel strangulation were reduced bowel wall enhancement on computed tomography (odds ratio 142.3, P<0.001), WBC greater than 12 000/mL (20.3, P<0.005), and guarding (14.9, P<0.005). Reduced bowel wall enhancement alone yielded a sensitivity of 56% and a specificity of 94% for bowel strangulation.

These results are consistent with two other small retrospective reviews of preoperative computed tomography imaging in patients who underwent laparotomy for small bowel obstruction, which reported that decreased bowel wall enhancement had a sensitivity of 33-78% and a specificity of 96-100% for bowel strangulation.[115 116] All three studies likely overestimated the sensitivity and specificity of computed tomography as a predictor of ischemia by selecting patients who were sick enough to be taken to the operating room. However, they highlight the relative importance of bowel wall hypo-enhancement in predicting transmural ischemia, even in the absence of peritonitis.

Clinical significance of pneumoperitoneum

Pneumoperitoneum in a patient who has not had recent surgery is suggestive of perforated viscus and deserves careful evaluation. However, the use of computed tomography has contributed to the increasing discovery of ever smaller volumes of pneumoperitoneum, and the clinical significance of these findings is unclear. A subset of these patients have developed pneumoperitoneum related to barotrauma or vaginal insufflation or may have small and self contained perforations.[117] Several small retrospective series suggest a non-therapeutic laparotomy rate of up to 13% of patients with pneumoperitoneum.[6]

In optimal circumstances, plain radiography can detect as little as 1 mm of free intra-peritoneal air.[118] However, compared with computed tomography, plain radiographs reportedly have a sensitivity of only 30-59% for free air.[119 120] By contrast, a large prospective analysis of 1723 patients with surgically proven hollow viscus perforation reported pneumoperitoneum in 89% of preoperative plain radiographs.[121] One possible explanation for the discrepancy is that computed tomography is so sensitive that it identifies pockets of pneumoperitoneum that are not clinically relevant.

In the absence of data to guide the clinician as to which patients with pneumoperitoneum can be safely observed, we recommend a low threshold for operative exploration in patients without recent operative intervention who are found to have pneumoperitoneum. All patients with generalized peritonitis or hemodynamic instability certainly warrant surgery. Patients with an incidental finding of pneumoperitoneum who are otherwise pain free and clinically stable and have a benign examination may be given a trial of conservative management but should be monitored

with serial abdominal examinations, laboratory studies, and potentially repeat imaging.

Pneumoperitoneum in the postoperative period presents a particular diagnostic challenge. A full discussion of diagnosis of postoperative complications is beyond the scope of this review, but the available data show that postoperative pneumoperitoneum is a common finding after both laparoscopy and laparotomy (40% of patients) and the volume of pneumoperitoneum steadily decreases up to one month postoperatively.[122-124] Compared with patients with normal postoperative pneumoperitoneum, those with anastomotic leaks tend to have larger initial volumes of pneumoperitoneum, which tend to increase rather than decrease over time and are more likely to be associated with radiographic evidence of ileus.[122-125]

Clinical significance of pneumatosis intestinalis

Pneumatosis intestinalis, the presence of gas in the bowel wall, may be a sign of bowel wall ischemia but is also associated with chronic obstructive pulmonary disease, asthma, tuberculosis enteritis, cystic fibrosis, and collagen vascular disease.[126] The pathophysiology of pneumatosis is poorly understood, but the leading hypotheses are that either gas dissects into the bowel wall owing to a pressure differential or that gas forming bacteria enter the bowel wall.[127] Distinguishing between benign and pathologic pneumatosis is challenging and important.

A recent prospective multicenter trial examined 127 adults who were found on computed tomography to have pneumatosis.[128] Investigators prospectively collected information on comorbidities, clinical presentation, and other imaging findings that might predict which patients with pneumatosis had or would develop transmural ischemia. Forty eight (38%) patients had pathologic pneumatosis defined as transmural ischemia during surgery or at autopsy. Patients in the pathologic pneumatosis group had a significantly higher overall mortality (34%) than the benign pneumatosis group (14%). In the multivariate analysis, the presence of peritonitis (odds ratio 35.8), lactate greater than 2 mmol/L (5.0), elevated international normalized ratio (4.1), and decreased hemoglobin (0.7) were all predictive of pathologic pneumatosis. Importantly, although peritonitis was the strongest predictor of pathologic pneumatosis, 80% of patients in the study did not have peritonitis on presentation. These findings are highlighted by another recent study which showed that pneumatosis intestinalis with an elevated lactate was associated with greater than 80% mortality.[129]

In summary, pneumatosis is a non-specific finding. We recommend a low threshold to surgically explore any patient who presents with pneumatosis and peritonitis and/or elevated lactate. However, patients with incidentally found pneumatosis who are otherwise stable with a benign abdominal examination can be observed.

Management

The principles of management of secondary peritonitis are fluid resuscitation, the use of empiric antibiotics, and control of the septic focus. Secondary peritonitis can lead to significant fluid sequestration and hypovolemia, which may be exacerbated by vomiting or diarrhea. The management of sepsis has been recently reviewed.[28] Here we will discuss the principles of intervention and the role of antimicrobial agents in the published guidelines, and discuss the emerging role of laparoscopic lavage.

Guidelines

Recent guidelines from the Infectious Diseases Society of America, World Society of Emergency Surgery, and Surviving Sepsis Campaign are in broad agreement with regard to the initial resuscitation and antibiotic management of patients with secondary peritonitis.[41-43] Patients with sepsis should receive immediate resuscitation with crystalloid with a goal of a central venous pressure of 8-12 mm Hg, a mean arterial pressure of at least 65 mm Hg, a urine output of at least 0.5 mL/kg/h, mixed venous oxygen saturation of 65%, and normalizing serum lactate. Patients with secondary peritonitis should be treated empirically with broad spectrum antibiotics including Gram positive, Gram negative, and aerobic coverage. In patients with sepsis or septic shock, antibiotics should be delivered within one hour. The selection of antimicrobial agent and recent national and international guidelines on antibiotic selection have been reviewed recently.[130] The decision to cover drug resistant organisms or to add empiric fungal coverage should be based on individual risk factors.[130] Patients with a history of solid organ transplant, with underlying pulmonary or liver disease, or with a duodenal source of peritonitis and postoperative patients with exposure to broad spectrum antibiotics within three months or preoperative hospital admission for longer than five days are all at increased risk of drug resistant organisms.[131-133] The appropriate use of empiric antifungal coverage is a topic of ongoing research but should be considered in critically ill patients with recurrent abdominal surgery or peritonitis secondary to anastomotic leak.[134 135]

Patients with generalized peritonitis or localized peritonitis with hemodynamic instability need urgent surgery. Guidelines differ as to whether a partially resuscitated patient should be taken directly to surgery,[41] or whether intervention should follow successful resuscitation.[136] However, the data cited in support of these statements depend primarily on the risk of failure of source control if intervention is delayed beyond 24 hours,[12 137-139] or the management of necrotizing soft tissue infections,[140-142] respectively. To our knowledge, only a single study has directly assessed the optimal timing of surgery for secondary peritonitis. One group carried out a prospective observational trial in which 154 patients who presented with septic shock and with evidence of gastrointestinal perforation on computed tomography were managed with an adapted early goal directed therapy algorithm and were taken to surgery as soon as the diagnosis was made, independent of their hemodynamic response to resuscitation.[143] The mean APACHE II score was 24 (SD 9), and 96% of patients in this group had gross contamination of three or four abdominal quadrants in the operating room. Patients underwent definitive surgical management with omental plication or bowel resection. Both SOFA score and time from admission to the start of surgery were independently associated with 60 day survival (odds ratio 0.80, 95% confidence interval 0.66 to 0.95, and 0.29, 0.16 to 0.47, per hour delay). However, despite the authors' stated intention to take patients directly to the

operating room as soon as a diagnosis was made, the time to surgery varied considerably (mean 3.1 (SD 1.5) hours). One must wonder whether this delay is explained, in part, by an inadequate response to resuscitation and, therefore, that it was a failure to respond to resuscitation and not a delay in intervention that led to increased mortality. Thus, we recommend aggressive resuscitation with a goal of hemodynamic stability before surgical intervention in patients with abdominal sepsis.

Emerging treatments

There has been considerable recent interest in identifying patients with a perforation that has sealed, but in whom the presence of succus in the abdomen continues to drive a septic response. The hope is that these patients could be treated with laparoscopic lavage without needing repair or resection of a gastrointestinal defect. Three recent RCTs have examined this approach in perforated diverticulitis, randomizing about 350 patients with purulent peritonitis to laparoscopic lavage or sigmoidectomy.[109-111] All three trials excluded hemodynamically unstable patients and those with feculent peritonitis. However, the LOLA and DIALA trials randomized patients after diagnostic laparoscopy, whereas the SCANDIV trial randomized patients after computed tomography scan. As a result, the SCANDIV group contained some patients with Hinchey I or II disease (table 3). No significant difference was seen in 30 day or 12 month mortality. Laparoscopic lavage was associated with significantly more reinterventions in the first 30 days. However, this included both reoperation and percutaneous drainage. According to data from LOLA and DIALA, which included 12 month follow-up, laparoscopic lavage was associated with significantly fewer reoperations within the first 12 months, but no difference existed in the number of patients with a stoma at 12 months or in complications.[45 46] The available data suggest that laparoscopic lavage is a reasonable approach in hemodynamically stable patients with purulent peritonitis from perforated diverticulitis. However, further studies will be needed to determine whether this approach can be applied to other sources of contamination.

When the degree of perforation or extent of contamination is unclear in secondary peritonitis, diagnostic laparoscopy is an option. In a small RCT, 120 patients with abdominal pain of unclear etiology and without peritonitis were randomized to early diagnostic laparoscopy or observation with surgical intervention if evidence of peritonitis developed. Twenty eight per cent of patients in the observation group developed peritonitis and needed surgery. Patients in the early diagnostic laparoscopy group had significantly fewer imaging studies and were more likely to have a definitive diagnosis at discharge. No difference was seen in 30 day mortality, readmission, or morbidity and no difference in length of hospital stay. However, median well-being score improved significantly more between admission and six weeks in the early laparoscopy group than in the observation group.[47] A second trial randomized 104 non-pregnant 15-45 year old women with acute non-specific right lower quadrant abdominal pain to early diagnostic laparoscopy or observation, and 39% of patients in the observation group needed surgery at the initial admission for progression of symptoms. No difference was seen in morbidity or mortality, but patients in the early laparoscopy group had significantly shorter length of stay in hospital (3.7 *v* 4.7 days; P=0.004) and were significantly more likely to have a definitive diagnosis at discharge. The authors reported significantly lower rates of recurrent abdominal pain in the early laparoscopy group at three months but no difference at 12 months.[48] No difference was seen in hospital costs between the two groups, including the cost of managing recurrent pain. These data highlight the diagnostic value of laparoscopy, but this approach is not yet the standard of care. As a result, in a patient with peritonitis, we suggest that once surgeons have committed to diagnostic laparoscopy, they are obliged to consider laparotomy if they are unable to determine the etiology of peritonitis.

HOW PATIENTS WERE INVOLVED IN THE MAKING OF THIS ARTICLE

A 73 year old woman who presented with acute abdominal pain, and was later found to have a malignant gastric outlet obstruction, and her husband kindly accepted an invitation to review the manuscript as patient reviewers for *The BMJ*. They were asked to identify which sections were the most relevant to their experience and which were the least useful and to suggest topics that were underemphasized. As a result of their input, we emphasized the importance of avoiding testing that would delay definitive diagnosis and clarified the need to avoid repeated exposure to ionizing radiation. The patient also asked us to emphasize how important it was to her that the results of all tests were shared with her and her family in a timely manner to improve their sense of control in a very difficult period.

RESEARCH QUESTIONS

- Does a biomarker exist that would reflect the degree of containment of intra-abdominal contamination?
- Do new, shorter, magnetic resonance imaging sequences have a role in the diagnosis of acute abdominal pain?
- What is the role of laparoscopic lavage in managing patients with ongoing sepsis but in whom the initial gastrointestinal defect seems to have sealed?
- What is the best next step in patients who undergo diagnostic laparoscopy without clear source of peritonitis? Can these patients be observed or must they have laparotomy?
- What is the role of non-operative management or percutaneous drainage for anastomotic leak?
- What are the differences in the epidemiology of secondary peritonitis between children and adults?

Conclusions

Secondary peritonitis remains an important clinical problem with considerable mortality. The degree to which a patient can contain intra-abdominal contamination and tolerate the associated systemic inflammatory response are the major determinants of the severity of secondary peritonitis and should be the major drivers in management decisions. Despite the wide range of laboratory and radiographic tests available and their utility in evaluation of abdominal pain, secondary peritonitis remains primarily a clinical diagnosis. No individual laboratory test is sufficient to identify which patients need surgical intervention or which are at risk of perforation due to strangulation or mesenteric ischemia. Impor-

tantly, the data do not support the use of serum lactate, base deficit, or white blood cell count to guide surgical intervention in secondary peritonitis or in identifying patients at high risk of perforation or ischemia. The widespread availability of imaging, particularly computed tomography, is valuable in the diagnosis of acute abdominal pain and critical to the identification of patients at high risk of perforation or ischemia. However, definitive management in a patient with generalized peritonitis should not be delayed in the hope of learning more about the source of the contamination. Management of secondary peritonitis has evolved substantially with the refinement of image guided percutaneous drainage and laparoscopy. Further studies will be needed to clarify the role of diagnostic laparoscopy and laparoscopic lavage.

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