The peritoneum and abdominal sepsis

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Abstract

Complicated intra-abdominal infections are an important cause of morbidity and may be associated with poor prognosis. The understanding of the pathophysiology of the peritoneum in the manifestation of abdominal sepsis and knowledge of the source of pathogenic organisms, which reach the peritoneal cavity, are crucial to the prevention of intra-abdominal surgical infection. The ability to identify the presence or absence of peritoneal inflammation probably has the greatest influence on the final surgical decision. This article reviewed the role and impact of the peritoneum in abdominal sepsis.

Introduction

Complicated intra-abdominal infections (cIAIs) are one of the most challenging situations in surgery and usually presents as peritonitis.[1] They are an important cause of morbidity and may be associated with a poor prognosis. Most cases of infective (bacterial) peritonitis are secondary to gastrointestinal disease. Primary infective peritonitis is usually due to *Escherichia coli* or *Streptococcus pneumoniae* in cirrhotic patients with ascites and hematogenous spread from a septic focus *e.g.*, osteomyelitis in children, hemodialysis patients and the immunocompromised. Infections such as amoebiasis and candidiasis can also cause primary peritonitis.[2] Intra-abdominal abscess may occur within an intra-abdominal organ. These include pyogenic abscess in the liver from portal pyaemia *e.g.,* following appendicitis or a perforation (now rare because of the use of antibiotics); pancreas from acute pancreatitis and in the fallopian tube (pyosalpinx) following adhesions in the fimbriae from an ascending infection.[1,3] Infection above an obstructing calculi may include empyema of the gall bladder or the renal pelvis.[4] This article reviewed the role of the peritoneum in abdominal sepsis.

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Anatomy and physiology of the peritoneum

The peritoneum comprises a serous membrane made of mesothelial cells lining the abdominal viscera (visceral layer) and separating it from the surrounding abdominal wall (parietal layer). The parietal and visceral parts are in continuity around the root of the viscus and are separated from each other by a cavity, which normally contains only a thin serous fluid that permits movement between the viscus and its surroundings.[5] The peritoneum has a large surface (2 m^2) that is almost equivalent to the total body surface area. Its semi-permeable membrane allows rapid two-way passive fluid transport of water and most solutes, and the lymphatics in the diaphragm actively absorb bacteria, fluids, particle and deformable particles as large as leucocytes. In the normal peritoneum there is rapid movement of fluids, bacteria and leucocytes along well-defined pathways around the peritoneum, through the diaphragmatic lymphatics to the mediastinal lymphatics and thence to the thoracic duct. This *dispersion* of infection is facilitated by the fibrinolytic activity of the peritoneum derived from mesothelial cells and submesothelial blood vessels. However, this activity is lost even after minor peritoneal injury resulting in rapid adhesion between affected surfaces. Therefore, peritoneal resistance depends on *localization* rather than *dispersion*.[6]

Pathophysiology of peritonitis

A complicated cIAI extends beyond the hollow viscus of origin into the peritoneal space and causes either localized or generalized peritonitis.

Localized peritonitis

Localized peritonitis implies either contained or early perforation of a viscus or inflammation of an organ in contact with anterior parietal peritoneum. It occurs because peritoneal resistance to infection relies upon localization rather than dispersal of a contaminant. The inhibition of peritoneal fibrinolysis permits stabilization of fibrinous exudates and limits the spread of infection. The omentum *abdominal policeman* is attracted to the inflammatory site and along with the intraperitoneal viscera have a remarkable ability to confine infection as seen, for example, in acute appendicitis, diverticulitis and the omental plugging of the perforated duodenal ulcer. For instance, a palpable mass in the right iliac fossa may represent either an inflamed mass of adherent omentum, appendix and adjacent viscera, or an abscess.[7]

Generalized peritonitis

Generalized peritonitis will occur when there is failure of localization. Failure of localization may arise for the following reasons: i) a rapid contamination that does not permit localization as in perforated colon/anastomotic leak; ii) persistent or repeated contamination that overwhelms an attempt to overcome it; iii) a localized abscess that continues to expand and ruptures into the peritoneal cavity (*e.g.*, appendix, diverticular abscess).[8-11] The peritoneal cavity becomes acutely inflamed with production of an inflammatory exudate, which spreads through the peritoneum leading to intestinal dilatation and paralytic ileus. The risk of generalized peritonitis secondary to appendicular perforation is greater in children in whom the host defenses including greater omentum are poorly developed, and the elderly in whom due to atherosclerosis, gangrene and perforation are common.[12-14] It may be difficult to reach the correct pre-operative diagnosis in patients with colonic perforations as they often present with generalized peritonitis. Although there may be clues in the history, the diagnosis is being established usually only at laparotomy.[15,16]

Microbiological aspects

Most cases of peritonitis are caused by organisms derived from the gastrointestinal tract, *i.e.*, endogenous. The contents of the stomach and duodenum are more sterile than the contents of the distal gut. Thus, the sequela of an upper gastrointestinal tract perforation is less severe than that of lower gastrointestinal tract, at least initially. The peritoneal fluid is initially sterile due to host defense mechanisms, but secondary bacterial invasion occurs within 6 h and bacterial peritonitis follows chemical peritonitis. Infection is enhanced by the synergy between aerobes *e.g.*, *E. coli*, which reduce oxygen content and facilitates growth of obligate anaerobes *e.g.*, *Bacteroides fragilis* and by the presence of adjuvant substances such as feces, bile or urine.[17] Untreated colonic perforation with fecal peritonitis is rapidly fatal because of the absorption of the high pathogenic bacteria load and their toxins from the peritoneal cavity causing septicemia. This would produce a rapid and profound systemic inflammatory response syndrome with consequent multiple organ failure to which the elderly easily succumbs.[18] Tuberculosis bacteria reach the gastrointestinal tract via hematogenous spread, ingestion of infected sputum, or direct spread from infected contiguous lymph nodes and fallopian tubes. Reactivation of disease in these nodes, especially in the immunocompromised including diabetes, renal failure and malignancy, may lead to abdominal tuberculosis (TB), with the spread of the bacteria to the peritoneum or intestine.[19]

Clinical assessment of peritonitis

Surgical peritonitis and intestinal obstruction are the two important causes of the acute abdomen. The acute abdomen is defined as the rapid onset of severe symptoms that may indicate potentially life-threatening intra-abdominal pathology that requires urgent surgical intervention. Surgical peritonitis may emanate from perforation, ischemia (mesenteric or strangulation), pancreatitis and anastomotic leakage. The aim of both the history and examination is to determine a diagnosis and clinical decision. A precise history of the acute abdomen may indicate the gastrointestinal pathology and physical examination may indicate where the pathology is. There are well established specific features associated with all acute abdominal conditions but it is the ability to identify the presence or absence of peritoneal inflammation, which probably has the greatest influence on the final surgical decision.[15] Conditions that start suddenly and produce signs of peritonitis are perforation of viscus (*e.g.*, peptic ulcer, typhoid, diverticulitis), infarction (embolus or volvulus), and intraperitoneal hemorrhage (*e.g.*, ruptured ectopic pregnancy, aortic aneurysm). The abdominal tenderness due to intra peritoneal blood has a different character and is less pronounced than that of peritoneal inflammation due to sepsis[9] Although the ultimate decision to operate must be based on clinical rather than radiological criteria, in acute diverticulitis or suspected anastomotic leakage, water-soluble contrast radiology may identify a *leak*, and computed tomography scanning may identify a collection which would influence the surgical decision including the guided-percutaneous drainage of the collection.[20] Perforation complicating toxic dilatation is more commonly due to undiagnosed ulcerative colitis than from infective (*Campylobacter spp., Yersinia enterocolitica* or *E. coli 0157*) colitis. In the latter common signs (pain and peritonism) are often few and masked by steroids and clinical suspicion and free gas on plain x-ray may give the diagnosis.[16,21]

Although acute severe abdominal pain is the hallmark of the acute abdomen, a pain-free acute abdomen may occur in older people, in children, in the immunocompromised, in the last trimester of pregnancy and in the patient in the Intensive Care Unit (ICU).[22-24]

Conditions that produce peritonitis of gradual onset usually arise from a progressively inflamed viscus as in acute appendicitis, cholecystitis, diverticulitis and gastrointestinal infections.

Acute appendicitis

Acute appendicitis is the most common cause of the acute abdomen requiring surgery with a life time risk of 7%, and it is one of a relatively dwindling number of conditions in which a decision to operate may be based solely on *clinical findings*.[9,10] The natural history if left untreated is that it will either resolve spontaneously by host defenses, or progress to a fatal suppurative necrosis (gangrene) with perforation. The appendicular artery is a single end artery closely applied to the wall distally, and secondary thrombosis is common giving rise to gangrene which explains the short progressive history (3-5 days) of appendicitis and the poorer prognosis in the atherosclerosis of the aged. The classical presentation is referred, dull, poorly localized, colicky periumbilical pain (visceral) from the luminal obstruction (mid-gut origin) for 12-24 h that shifts and localizes to the right iliac fossa at *McBurney's point* where peritoneal irritation by the inflamed appendix occurs (somatic pain). This is akin to the non-specific visceral pain of biliary colic in the epigastrium (fore-gut origin) and the later constant somatic pain of acute cholecystitis as the parietal peritoneum is irritated. This is manifested as pain on palpation of the fundus of the gall-bladder underlying the 9th costocartilage on deep inspiration (Murphy's sign).[25] An alternative outcome is that the appendix becomes surrounded by a mass of omentum or adjacent viscera which walls off the inflammatory process and prevents inflammation spreading to the abdominal cavity yet resolution of the condition is delayed (appendix mass). Such a patient usually presents with a longer history (a week or more) of right lower quadrant abdominal pain, appears systemically well and has a tender palpable mass in the right iliac fossa. Sub-acute small bowel obstruction may occur and in the elderly the appendix mass may be confused with a cecal carcinoma, ileocecal lymphoma, Crohn's disease, ileocecal tuberculosis, or an ovarian tumor.[10] Conservative management risks a 30% recurrence of acute inflammation.[26,27] As an appendix mass is often detected only after the patient has been anaesthetized and paralyzed, the differentiation of a phlegmonous mass from an abscess is not a practical problem because surgery is the correct management for both. Operation during the first admission can be expeditious and safe, provided steps are taken to minimize postoperative sepsis. Such a policy would render any debate on interval appendicectomy redundant. The consequences of missing a carcinoma in the elderly patient or other pathology are also abolished.[10]

The dilemma

Occasionally, fluid leaking from a perforated peptic ulcer down the right paracolic gutter produces clinical findings resembling those of acute appendicitis. A classical appendicectomy incision would reveal

bile-staining free peritoneal fluid and a second upper abdominal incision is usually required. Purulent fluid tracking down the right paracolic gutter may also suggest acute cholecystitis. If clinical diagnosis is equivocal despite investigations, it is best to begin with a low midline incision which could be extended if there is evidence of a perforated peptic ulcer.[10] It is not surprising that women have the highest appendicectomy rate with 30% revealing normal appendices.[28,29] In young women, various gynecological conditions present with lower abdominal pain, and the gynecological history gives important clues. The condition of *Curtis-Fitz-Hugh syndrome*, when transperitoneal spread of pelvic inflammatory disease produces right upper quadrant pain due to perihepatic adhesions, is now well recognized and care must be taken to distinguish this from acute biliary conditions.[3,29] Early recognition with diagnostic laparoscopy and appropriate treatment of pelvic inflammatory disease may help to avoid potentially serious longer term sequelae.[30] A right tubo-ovarian abscess may mimic an appendix abscess in a young woman, and many studies have now demonstrated that laparoscopy significantly improves surgical decision-making especially in young female patients with acute abdominal pain.[7,30] Interestingly, studies suggest that whereas surgery may be associated with adhesions, subsequent tubal infertility is only adversely affected in patients with perforated appendicitis.[31]

In pregnancy, the enlarging uterus progressively displaces the appendix up into the right hypochondrium. Difficulty in diagnosis, reluctance to operate on pregnant women and avoidable delay count for the high risks of appendicitis in pregnancy. Delay is so harmful to mother and unborn child that provided urinary tract infection has been excluded one should operate early. Maternal and fetal deaths do not result from appendicectomy but from peritonitis following perforation. The risk of maternal mortality increases as pregnancy progresses.[23,28]

Determining whether or not an unstable patient in ICU has an abdominal process, which requires intervention, can be difficult as the usual signs may be absent due to sedation and paralysis. Distention, appearances of wounds, stomas drain effluent and any systemic deterioration may give clues. Joint management (intensivist, surgeon and the radiologist) offers the best chance of success.[22,32] Further surgical intervention for an unstable patient with a recurrent problem *e.g.*, further sepsis in patient with recent fecal peritonitis or a new complication *e.g.*, acalculous cholecystitis in patient with a head injury can be hazardous yet vital.[32] Even in the former case, there may usually be alternative sources of sepsis (chest, urine, lines, *etc.*), which need treatment with no less urgency. However, missed significant abdominal sepsis in a patient with organ failure is almost always fatal.[32] The aim is to operate in a timely manner on as well prepared a patient as possible although it may not be able to make the patient stable until the underlying cause is dealt with.[1,4,32-35]

Acute tropical gastrointestinal infections

Typhoid (enteric) fever

Typhoid (enteric) fever is a common water-borne disease in the developing world, generally transmitted via the fecal-oral route and the causative organism being the bacterium *Salmonella typhi*. If untreated or undiagnosed, intestinal perforation usually in the third week of illness is a serious complication.[36,37] More than 50% of typhoid ileal perforations occur in children with a peak age of 5-9 years.[38,39] The preoperative diagnosis of typhoid ulcer perforation can be difficult being often clinical, based on the history and features of peritonitis. Most typhoid perforations present insidiously because loops of diseased gut stick together, so that leaking gut contents do not spread widely and sometimes the leak is small.[37] Perforations in patients on typhoid treatment inside the hospital are easily missed if not suspected. The high incidence of perforation has been attributed to late diagnosis and the emergence of multi-drug resistant virulent strains of *Salmonella typhi*.[40] The high mortality (>20%) is due to the combination of typhoid disease and the sequelae of intestinal perforation which must both be adequately treated.[41] The prognosis is poor in patients with ongoing HIV enteropathy and not on antiretroviral treatment.[37,42]

Tuberculous peritonitis

Intestinal TB is caused by *Mycobacterium tuberculosis* or *M. bovis* after ingestion (swallowed sputum or infected milk), or after blood-borne spread from another focus. Tuberculous peritonitis is usually due to reactivation of a tuberculous focus in the peritoneum with concurrent pulmonary, intestinal or genital TB (especially from the fallopian tubes).[43,44] It is usually seen in debilitated patients and alcoholics but the incidence of peritoneal TB is increasing in European countries due to the continued immigration of people from endemic areas affected by tuberculosis.[43] Peritoneal tuberculosis occurs in three forms: wet type with ascites, dry type with adhesions, and fibrotic type with omental thickening and loculated ascites.[19] The diagnosis of peritoneal TB is easily made at laparotomy with the characteristic tubercles that appear as white *seedlings* on the parietal and visceral surfaces of the peritoneum. Inflammation and exudation leads to the formation of straw-colored ascites.[45] In some cases there is associated infiltration and thickening of the omentum, thickening of the intestinal walls, and formation of caseous masses - the condition sometimes referred to as *plastic* peritonitis. The histology shows classic granulomas, often caseation, but not always with demonstrable acid-fast bacilli.[46] Due to the efficacy of quadruple therapy for 2 months (isoniazid 300 mg/day, rifampicin 450 mg/day, pyrazinamide 1250 mg/day, ethambutol 750 mg/day, for a 50-kg patient; followed by isoniazid and rifampicin alone for 4 months), surgery for intestinal TB is only indicated for complications such as obstruction, hemorrhage or perforation.[47]

Amoebiasis (*Entamoeba histolytica* infection)

Amoebiasis is caused by the enteric dwelling protozoa, *Entamoeba histolytica.* It is endemic in the developing world, transmitted through the fecal-oral route and may or may not be symptomatic. Although <90% are asymptomatic, amoebic dysentery is similar to ulcerative colitis with colorectal mucosal invasion (proctocolitis) causing a bloody diarrhea or, rarely, a fulminant course with a bad prognosis. The non-dysenteric colonic disease - strictures, an inflammatory mass (amoeboma), appendicitis, abscess, perianal or skip lesions are less common, but can simulate Crohn's disease. Invasive amoebiasis-hepatic abscess (acutely or focally tender hepatomegaly in an ill patient) is derived from the colon via the inferior mesenteric and portal veins may rupture into the pleural, peritoneal, or pericardial cavity, with serious consequences if not adequately drained.[48,49] Pregnant women, small children, and those immunosuppressed by steroid therapy are at particular risk of invasive amoebiasis suggesting the relevance of cell mediated immunity especially as cytotoxic T cells and activated macrophages are capable of killing amoebae *in vitro.*[48,50] However, HIV patients seldom suffer from invasive amoebiasis. Thus, a deficiency of T helper cells seems to be insufficient to promote invasion or HIV infection inhibits colonization by pathogenic strains.[51] The parasite invasion of human cells is mediated by galactose-binding (Gal/GalNAc) surface lectin. Gal-lectin based vaccinations have conferred protection in various animal models against *E. histolytica* infections. Thus, a framework for the future human amoebiasis vaccine.[52]

Invasive amoebiasis (but not the passing of *cysts per se*) results in high levels of circulating anti-amoeba serology, which is the basis of the very useful serodiagnostic test.

Sepsis scoring systems

Many scoring systems have been created for assessing patient risk of death during an event of peritonitis. The *Mannheim peritonitis index score* (MPI) is a reliable predictor of the peritonitis outcome as the increase of MPI scores is proportional to that of morbidity and mortality. MPI adverse factors include presence of organ failure, time elapsed >24 h before surgery, presence of malignancy, origin of sepsis, the presence of fecal peritonitis and generalized peritonitis.[53,54] The *World Society of Emergency Surgery Severity Sepsis Score* is the new practical sepsis severity score for patients with cIAIs. With a high sensitivity (89.2%) and specificity (83.5%) the clinical conditions of the diagnosis (severe sepsis and septic shock) the origin of the cIAIs, the delay in source control, the setting of acquisition and risk factors, such as age and immunosuppression, were independent predictors of the mortality of sepsis during hospitalization.[55]

Source control

Source control eliminates infectious foci and controls factors that promote on-going infection. Source control failure is more likely in patients with delayed (>24 h) procedural intervention, higher severity of illness (APACHE>15), advanced age, comorbidity, poor nutritional status and a higher degree of peritoneal involvement (*i.e.*, a high MPI score), and heralded by persistent or recurrent intra-abdominal infection, anastomotic failure or fistula formation.[4] A better understanding about susceptibility to infections (patient factor) will explain why a patient with minimal bacterial contamination at surgery may develop a pelvic abscess whereas another patient with massive fecal contamination after stercoral perforation of the colon may not develop infective complications. Inter-individual variation in the pattern of mediator release and of end-organ responsiveness may play a significant role in determining the initial physiological response to major sepsis and this in turn may be a key determinant of outcome.[1] Other key determinants are the initial severity of infection *e.g.*, colonic perforation, the timeliness and adequacy of attempts at treatment.[53,54] Early definitive primary or re-operative surgery leading to the removal of necrotic tissue, the drainage of abscesses, and the control of peritoneal soilage (source control) is crucial in the intra-abdominally septic patient.[4,55] Ongoing intestinal ischemia with doubt about intestinal viability is best managed by exteriorizing the bowel ends after resection of the ischemic bowel and a second-look laparotomy undertaken 24-48 h later.[1,35] Laparotomy as opposed to primary closure of abdominal fascia may be indicated if there is a risk of developing an abdominal compartment syndrome from severe sepsis and septic shock.[34,35] Generalized peritonitis from perforated appendicitis, which has been diagnosed preoperatively should be dealt with by formal laparotomy, rather than by making a gridiron incision, so as to allow thorough peritoneal toilet and lavage.[10] Contamination of the abdominal wall may be minimized by elevating the abdominal wall and aspirating pus and contaminated peritoneal fluid via a small incision in the peritoneum before it percolates over and inoculates the wound.[11,56]

Treatment options

It is not possible to practice fully the ideal management of early diagnosis and surgery for the acute abdomen, thus reducing the morbidity and mortality to zero, because patients and the disease are variable. However, because infections, inadequate tissue perfusion and a persistent inflammatory state are the most important risk factors for development of multiple organ failure, it is logical that initial therapeutic efforts are directed at their early treatment or prevention (early goal-directed therapy).[57,58] All patients should be resuscitated with intravenous fluids and adequate analgesia. Narcotic analgesia may assist diagnosis by relieving the patient's anxiety. Patient mortality is significantly lowered following early initiation of broad-spectrum antibiotics.[59,60] The principles in the management of the acute abdomen are to distinguish: i) if surgery is inevitable from the outset following diagnosis; ii) if there is no improvement or a worsening clinical condition; and iii) if the acute abdomen is responding well to conservative measures. Surgery is inevitable, for pathologies such as a perforated peptic ulcer, perforated intestinal typhoid, leaking aortic aneurysm, and a mesenteric ischemia, which may also require a second look laparotomy. Conservative management is limited to the resuscitation necessary in optimizing the patient's condition prior to operation. In the second scenario where the patient is not improving or has worsening clinical conditions, the initial diagnosis may have been incorrect, or a complication may have supervened such as the rupture of a diverticular pericolic abscess causing generalized peritonitis. The patient would require aggressive resuscitation in ICU and optimization prior to surgical intervention (resection and primary anastomosis in selected patients).[11,32,61,62] Treatment of diverticulitis has evolved towards more conservative and minimally invasive strategies.[63] Diverticular abscesses (about 5% of patients) may require percutaneous drainage if conservative treatment (antibiotics alone) fail.[8,64] In purulent peritonitis of diverticular origin (Hinchey Stage III and IV) laparoscopic lavage drainage could be considered particularly in elderly, unfit patients.[63,65]

In the third scenario, the patient responding to conservative measures may have pathologies such as acute cholecystitis, pancreatitis that respond to conservative medical management. However, a favorable initial response to conservative treatment may also indicate adequate resuscitation and optimization of a patient with a perforated viscus *e.g.*, peptic ulcer, anastomotic leak and now being rendered a window for surgical intervention. Any delay would lead to a loss of the benefits of resuscitation as sepsis supervenes.[1,9,11] Patients who might be considered for non-operative treatment of their perforation or anastomotic leak should have a contrast meal to confirm spontaneous sealing of the perforation.[66-68]

Is there a role for the abdominal drain?

It is generally futile to attempt to drain an anastomosis or the general peritoneal cavity as an enterocutaneous fistula may ensue.[1] The evidence is that drains may cause more problems than they solve if they are placed *just in case* of a leak. The adhesions that occur in the healing process of the anastomosis or general peritoneal cavity will attract the peritoneal drain (foreign body), which may physically damage the anastomosis or small bowel.[6] Secondly, the anastomosis needs to gain some extra blood supply, which it does by forming adhesions to adjacent vascular structures. If a piece of corrugated plastic is placed beside an anastomosis it will be unable to do this and a leak will be encouraged. The only exceptions to this are where the anastomosis is not watertight, such as with bile and urine, and a collection will interfere with healing.[69] Most surgeons are wary of the potential danger suction may do to an anastomosis. Redivac drains are deliberately not placed in the vicinity of anastomoses and are removed after 48 h.[70] Drains can mislead the surgeon as they easily get blocked. It is preferable for an anastomotic leak to reveal itself so that it can be managed accordingly. If there is no drain you can tell if an anastomosis has leaked by clinical signs backed by a water-soluble contrast study.[69] Large bore drains are useful in sepsis following inadequate peritoneal lavage or residual sepsis but should be placed in the appropriate dependent areas of the abdominal cavity such as the paracolic gutters, pelvis and subphrenic spaces away from the intestine.[1]

Conclusions

cIAIs describe a wide heterogeneity of patient populations, making it difficult to suggest a general treatment regimen and stressing the need of an individualized approach to decision making. It is the abil-

ity to identify the presence of peritoneal inflammation that probably has the greatest influence on the final surgical decision. Peritoneal sepsis is, however, not the sole cause of death but compounds comorbidities.

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