

## Management of abdominal sepsis — a paradigm shift?

Ari Leppäniemi<sup>1</sup>, Edward J. Kimball<sup>2</sup>, Inneke De laet<sup>3</sup>,  
Manu L.N.G. Malbrain<sup>3</sup>, Zsolt J. Balogh<sup>4</sup>, Jan J. De Waele<sup>5</sup>

<sup>1</sup>*Meilahti hospital, Abdominal Center, University of Helsinki, Finland*

<sup>2</sup>*University of Utah Health Sciences Center, Salt Lake City, Utah, USA*

<sup>3</sup>*Intensive Care Unit and High Care Burn Unit, Ziekenhuis Netwerk Antwerpen,  
ZNA Stuivenberg Hospital, Antwerp, Belgium*

<sup>4</sup>*Department of Traumatology, John Hunter hospital and University of Newcastle, Australia*

<sup>5</sup>*Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium*

### Abstract

The abdomen is the second most common source of sepsis and secondary peritonitis. The most common causes of abdominal sepsis are perforation, ischemic necrosis or penetrating injury to the abdominal viscera. Management consists of control of the infection source, restoration of gastrointestinal tract (GI) function, systemic antimicrobial therapy and support of organ function. Mortality after secondary peritonitis is still high. Excluding patient-related factors such as age or co-morbidities that can not be influenced at the time of intervention, delay to surgical intervention and inability to obtain source control are the main determinants of outcome. In patients with severe physiological derangement or difficult intraperitoneal conditions, where a prolonged operation and complete anatomical repair may not be possible or appropriate, it is becoming increasingly popular to utilize a damage control strategy with abbreviated laparotomy and planned reoperations. The main components of damage control laparotomy for secondary peritonitis are postponing the reconstruction of intestinal anastomoses to a second operation (deferred anastomosis) and leaving the abdomen open with some form of temporary abdominal closure (TAC). Advances in the management techniques of the open abdomen and new negative pressure-based TAC-devices have significantly reduced the previously observed prohibitive morbidity associated with open abdomens. These advancements have led to current fascial closure rates after TAC approaching 90%. The cornerstones of appropriate antimicrobial therapy are the timing, spectrum and dosing of antibiotics. Enteral nutrition should be started as soon as possible in hemodynamically stable patients but withheld when the patient is on a significant dose of vasopressors or whenever GI hypoperfusion is suspected. Timely source control with appropriate use of antimicrobial agents and early intensive care offers the best chance of survival for patients with abdominal sepsis. The introduction of the concept of damage control to the management of secondary peritonitis represents a paradigm shift in the same way as in management of major trauma. Although limited and repeated surgical interventions have been shown to be safe, the actual benefits need to be demonstrated in controlled studies.

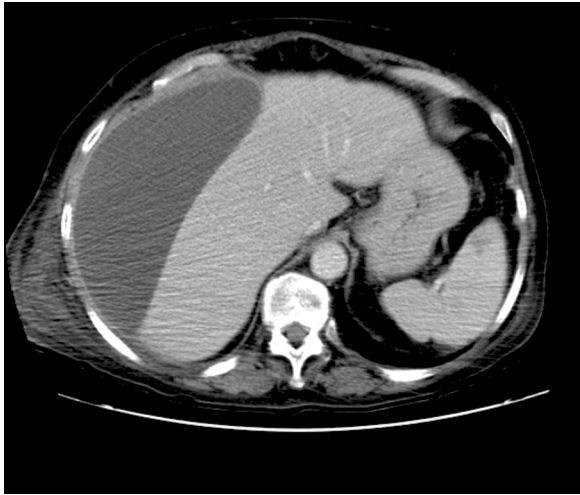
**Key words:** abdominal sepsis; intra-abdominal infection; damage control

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Following pulmonary sepsis, abdominal sepsis is the second most common form of sepsis requiring intensive care unit (ICU) management. In a nation-wide survey of ICU-treat-

ed adults with severe sepsis in Finland, an intra-abdominal source was found in 32% of patients and was associated with a hospital mortality rate of 32% [1].

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**Figure 1.** CT of a patient with subphrenic abscess after cholecystectomy



**Figure 2.** Operative photo of the same patient with subphrenic abscess

When systemic inflammatory response syndrome (SIRS) is due to infection, it is termed sepsis, and sepsis caused by an intra-abdominal infection (IAI) is termed abdominal sepsis. Sepsis with acute dysfunction of at least one organ is called severe sepsis, and severe sepsis with hemodynamic instability refractory to fluid administration, with a requirement for vasopressor support is termed septic shock [2].

In uncomplicated forms of IAI, the infection is contained within a single organ and rarely causes critical illness. Complicated IAIs extend beyond the source organ and into the peritoneal cavity and may progress to sepsis in approximately 40% of patients [2]. Contained infection results in the formation of an intra-abdominal abscess (Figs 1–2), whereas uncontained spread of infection leads to diffuse peritonitis.

Peritonitis is defined according to both its cause and extent and is usually divided into primary, secondary and tertiary peritonitis [2]. In primary peritonitis, there is no iden-



**Figure 3.** Peritoneal lavage

tifiable anatomic derangement of intra-abdominal viscera, whereas in secondary peritonitis the cause of the infection is in the abdominal viscera, as a consequence of either perforation, ischemic necrosis or penetrating injury. Tertiary peritonitis refers to situations where there has been no recovery from secondary peritonitis despite timely surgical intervention and appropriate antibiotics, and is sometimes associated with impaired host defenses.

A multicenter investigation performed in 68 medical institutions in Europe over a 6-month period identified a total of 2,152 patients with complicated intra-abdominal infections with an overall mortality rate of 7.5% [3]. The independent variables predictive of mortality included patient age, presence of an intestinal non-appendicular source of infection, intervention delay exceeding 24 hours, sepsis and septic shock in the immediate postoperative period, and ICU admission.

In another worldwide survey on complicated intra-abdominal infections performed by the World Society of Emergency Surgery, 88% of the infectious episodes were community acquired and the remaining were nosocomial intra-abdominal infections [4]. Generalized peritonitis was observed in 43%, and 57% of the patients had localized peritonitis or abscesses. The overall mortality rate was 10%.

The basic principles in managing abdominal sepsis include source control, restoration of GI function, systemic antimicrobial therapy and support of organ function [2]. Source control consists of eliminating the source of the leakage by suturing or resecting the leak site, and evacuating enteral content and pus by performing peritoneal lavage (Fig. 3). Although the prognosis of uncomplicated IAIs is good, in patients with severe sepsis or septic shock secondary to IAI, the mortality rate is about 25–35%, and may exceed 70%. A multitude of factors have been associated with mortality in secondary peritonitis such as shock, age, increasing APACHE II score, isolation of enterococci, impaired consciousness, inadequate empiric antibiotics,

poor nutritional status, cardiovascular disease, immunosuppression, hypoalbuminemia, thrombocytopenia, diffuse vs. localized peritonitis, subsequent nosocomial infection and a protein C concentration below 66% of normal [2]. Additional factors that have been identified such as elevated C-reactive protein (CRP) in the early postoperative phase [5] and an admission Sequential Organ Failure Assessment (SOFA) score for ICU patients [6], have prognostic significance specifically in severe secondary peritonitis.

Although most of these factors can not be influenced at the time of admission, there are two critical factors at the initial stages of sepsis that have a profound effect on survival and are the main focus of this review: a delay of definitive intervention more than 24 hours after symptoms started, and an inability to obtain source control at surgery. While the preoperative delay can be shortened with accurate diagnostics and rapid access to surgical care, these areas for improvement are beyond the scope of this review. The ability to achieve source control during the initial operation, the patient's inability to tolerate extensive and prolonged surgical intervention, and the general options for surgical and intensive care will be further discussed below.

## DAMAGE CONTROL

Various terminology including *staged abdominal repair*, *abbreviated laparotomy and planned reoperation*, and *open abdomen* have been applied in describing a surgical strategy where an external trauma, acute disease processes or a (surgical) complication has lead to a severe physiological derangement of the patient. Occasionally the management of severe cases can require such extensive and prolonged surgery that some patients may succumb intraoperatively. In managing such severe cases the damage control approach allows for temporary control of the source of insult (whether bleeding or contamination) [7]. Leaving the abdomen open allows for the patient to be transferred to an ICU for restoration of homeostasis followed by return to the operation theatre 1–2 days later for the definitive repair of organ defects.

The first damage control maneuver described in the literature was the packing of the liver to control bleeding from hepatic lacerations. Pringle in 1908 and Halsted in 1913 published the earliest descriptions of perihepatic packing for liver injury with severe bleeding [8, 9]. These observations were forgotten for several decades, until Stone and his co-workers published a series of 17 severely injured patients treated with abbreviated laparotomy and planned reoperation with a survival rate of 76% when compared with 14 similar patients undergoing definitive repair with only one survivor (7%) [10]. Damage control indications and techniques were refined by Ivatury in 1986 [11] and Burch in 1992 [12]. However, the term “damage control” — originat-



Figure 4. Measuring intra-abdominal pressure

ing from naval warfare, where the water leak in a ship hit by hostile fire was temporary controlled with any available means to enable the ship to keep mobile and evade further damage — was first used by Rotondo, Schwab and their co-workers in 1993 [13].

The principles of damage control surgery — early temporizing operation, leaving the abdomen open and planned reoperation with definitive repair — has recently been extended to other non-trauma surgical emergencies, such as the management of secondary peritonitis from bowel perforation, bowel ischemia, ruptured abdominal aortic aneurysm, and severe acute pancreatitis [14, 15].

In patients with secondary peritonitis, antibiotic loading and fluid resuscitation before laparotomy has beneficial effects on outcomes and these benefits are seen even for abbreviated surgical procedures [16–19]. This is fundamentally different from trauma and bleeding where there is often no time for resuscitation before surgery.

In peritonitis, a staged approach may be required for three different or often combined reasons:

First, the septic source cannot be controlled adequately with a single operation. Instead of the traditional model of one definitive operation and possible reoperation only performed as needed (relaparotomy on-demand [ROD] strategy), there are two other options to manage a severely contaminated peritoneal cavity. One, termed planned relaparotomy (PR), refers to a technique where the need for a second operation is recognized during the initial operation. Another option, the open abdomen (OA) technique, refers to leaving the abdomen open and treating the infected peritoneal cavity like an “open abscess” with frequent irrigations and temporary abdominal closure (TAC) techniques.

Second, the patient does not tolerate definitive repair and/or abdominal wall closure. In this scenario, the operation is deliberately abbreviated due to the severe physiological derangement and suboptimal local conditions for heal-

ing. Restoration of intestinal continuity is therefore deferred to the second operation (deferred anastomosis technique).

Third, the presence of extensive visceral edema (and occasionally packs left in the abdominal cavity for temporary hemorrhage control) may risk the development of abdominal compartment syndrome (ACS), if primary fascial closure is attempted (Fig. 4). To prevent ACS, the abdominal incision is left open and the viscera are covered with one of the TAC methods. ACS can develop from a number of complications related to intra-abdominal sepsis including, but not limited to, large volume fluid resuscitation resulting in visceral edema and intra-abdominal free fluid collection; retroperitoneal, intra-abdominal and abdominal wall bleeding; ileus; pseudo-obstruction and mechanical obstruction of the bowel.

### SOURCE CONTROL IN ABDOMINAL SEPSIS

Source control is defined as any and all physical means necessary to eradicate a focus of infection, as well as the modification of factors that maintain infection, such as leaking intestinal contents [2]. Source control is based on four principles: drainage, decompression, debridement and restoration of anatomy and function. All four principles can be applied independently, and at different moments in a single patient. In generalized peritonitis, laparotomy is the principal method to achieve source control. In patients where sepsis is caused by a perforation in the gastrointestinal tract, the aim of source control is to eliminate ongoing leakage of luminal contents through the removal of the perforation or through the creation of a controlled sinus or fistula [20].

In abdominal sepsis a single operation is not always sufficient to achieve source control and even if source control is achieved, a significant number of patients will develop complications necessitating a repeat laparotomy. Repeat laparotomy after any kind of abdominal surgery is required in about 2% of cases with the most common reason being leakage from an intestinal repair or anastomosis. In a series of 114 repeat laparotomies after abdominal surgery, intestinal leak was responsible for 30% of the reoperations with a mortality rate of 31% [21]. Postoperative peritonitis is associated with a mortality rate of 22–55% and is caused by the inability to control the septic source or clear the abdominal infection. Increased age and unconsciousness also contribute to this significant mortality rate [22]. Patients with duodenal leaks or fecal peritonitis are examples of conditions where it is sometimes difficult to achieve reliable source control

Because of the high mortality associated with secondary peritonitis especially in patients with inadequate source control, alternative strategies to a single operation with definitive repair and reoperations only as needed (ROD) were developed and include the PR and open abdomen

(OA) strategies. Although a meta-analysis comparing ROD and PR was inconclusive [23], a retrospective analysis of 278 patients by the same group showed that ROD was associated with higher in-hospital and long term survival rates, and was an independent predictor of survival [24]. A randomized study of 232 patients comparing these two treatment strategies showed no significant difference in the combination end point of all-cause mortality and major disease-related morbidity in surviving patients within a 12-month follow-up after index laparotomy [25]. However, there was a substantial reduction in repeat laparotomies, health care utilization and medical costs with ROD.

It appears that PR does not improve outcome over ROD and may even aggravate the inflammatory response [26]. In addition, PR should be used with caution in patients with duodenal leaks [27].

During the 1970s OA or laparostomy became one of the options to manage severe secondary peritonitis. Obviously, laparostomy does not obviate the need for abdominal re-explorations which, in turn, are facilitated by leaving the abdomen open [28]. Prior to the development of modern TAC methods [29], bleeding, and especially enteric fistula complications, were common and mortality was close to 40% [30, 31]. A randomized study comparing an obscure technique of OA (with nonabsorbable mesh and ROD) and the standard closed abdomen technique in severe secondary peritonitis was terminated at the first interim analysis due to higher mortality (55% vs. 30%) in the OA group [32].

Recent studies utilizing laparostomy with vacuum-assisted closure methods in secondary peritonitis have shown that the technique is safe and is associated with a relatively high (up to 75%) fascial closure rate 33–36. Adding some form of mechanical traction to the vacuum-therapy seems to further increase the fascial closure rate in abdominal sepsis [37], as has been shown in other abdominal emergencies requiring OA to treat or prevent ACS, such as in severe acute pancreatitis and abdominal vascular emergencies [38–40]. Whether OA with modern TAC methods helps to clear the infection, attenuate the peritoneal inflammation, reduce the risk of organ failure and improve outcome is still controversial, but experimental data seems to point towards improved outcomes [41]. Clinical studies, however, have been equivocal. Although a systematic review of the literature on this topic found the overall evidence to be of poor quality but reported the highest closure rates and lowest fistula rates in patients treated with NPT combined with fascial traction [42].

More recently, Kirkpatrick *et al.* [43] randomized 45 patients (about half of them undergoing laparotomy for intra-abdominal infection) after abbreviated laparotomy to NPT or Barker vacuum pack TAC and could not find any differences in inflammatory mediators.



## ABBREVIATED LAPAROTOMY AND DEFERRED ANASTOMOSIS

In a retrospective cohort study from Cali, Colombia, 112 patients with secondary peritonitis requiring bowel resection and managed with staged laparotomy were analyzed [44]. Deferred primary anastomosis was used in 34 patients where the bowel ends were ligated at the first operation and definitive anastomoses were reconstructed at the subsequent operation following physiological stabilization in the ICU and repeated peritoneal washes until the septic source was controlled. In contrast, 78 patients underwent enteral or colonic diversion followed by similar ICU stabilization and peritoneal washes. In both groups, the abdomens were left open at the initial operation and a Velcro system or vacuum pack was used for temporary abdominal closure.

The mean number of laparotomies was four in both groups. There were more patients with colon resections in the diversion group (80% vs. 47%). There was no significant difference in hospital mortality (12% for deferred anastomosis vs. 17% for diversion), frequency of anastomotic leaks or fistulas (9% vs. 5%), or acute respiratory distress syndrome (ARDS) (18% vs. 31%). The authors concluded that in critically ill patients with severe secondary peritonitis managed with staged laparotomies, deferred primary anastomosis can be performed safely as long as adequate control of the septic foci and restoration of deranged physiology is achieved prior to reconstruction.

Because this non-randomized study compared essentially two different damage control techniques (control of contamination with temporary bowel ligation or diversion, and leaving the abdomen open), it does not answer the fundamental question of whether it is better to perform primary anastomosis at the initial operation or during a subsequent operation. What it does show, however, is that the deferred anastomosis technique is not associated with a prohibitive rate of anastomotic leak when compared with leaks or fistulas associated with “semi-permanent” diversion.

In a non-randomized study of 27 consecutive patients with perforated diverticulitis (Hinchey III/IV), the patients were managed as follows: either with sigmoid resection and primary anastomosis ( $n = 6$ ), limited sigmoid resection or suture, open abdomen and primary anastomosis or colostomy at the second operation 24–48 hours later ( $n = 15$ ), or the Hartmann procedure; sigmoid resection and end colostomy ( $n = 6$ ) [45]. Although all 6 patients with primary anastomosis survived without complications, there was an obvious selection bias. Of the 6 patients undergoing Hartmann's procedure, one died of sepsis and 5 were discharged with a stoma. In the interesting group of 15 patients with deferred anastomosis or stoma and open abdomen, 9 patients had intestinal continuity restored during the

second look operation with one fatal anastomotic leak. In addition, there were two patients with dehiscence of the abdominal closure and death from pneumonia and multiple organ failure, respectively.

In a prospective study of 51 patients with perforated diverticulitis (Hinchey III/IV), patients were initially managed with limited resection, lavage and TAC with vacuum-assisted closure followed by second, reconstructive operation 24–48 hours later [46]. Bowel continuity was restored in 38 patients, with 4 protected by a loop ileostomy. Five anastomotic leaks (13%) were encountered requiring loop ileostomy (2 patients) or Hartmann's procedure (3 patients). Postoperative abscesses were seen in 4 patients, and one case each of abdominal wall dehiscence and relaparotomy for drain-related small bowel perforation. The overall mortality rate was 10% and 35/46 (76%) of the surviving patients left the hospital with reconstructed colon continuity. Fascial closure was achieved in all patients.

It seems that the concept of damage control with lavage, limited bowel resection, open abdomen and delayed anastomosis is feasible in selected patients with secondary peritonitis after a sigmoid perforation. However, more studies are needed to examine the safety and potential benefit of deferring the construction of intestinal anastomoses to a later stage (after open abdomen) in patients with generalized secondary peritonitis for perforated diverticulitis, as well as other causes.

## ABDOMINAL COMPARTMENT SYNDROME AND ABDOMINAL SEPSIS

The incidence of intra-abdominal hypertension (IAH) or ACS in patients with secondary peritonitis is not known [47]. The etiology of IAH and ACS is multifactorial, and the initiation point of the septic process is impossible to describe. This makes the abdominal sepsis associated IAH/ACS very difficult to characterize and predict in a timely fashion in comparison to post-injury ACS where the time of the injury and the beginning of the resuscitation have well-defined starting points. Generally, the clinical starting point for severe abdominal sepsis is arbitrarily assigned to the time of definitive diagnosis (frequently surgery) or the time of ICU admission due to physiological derangements.

In addition to the potential beneficial effects seen with the open abdomen combined with topical negative pressure (including reducing the inflammatory response and clearing the infection), leaving the abdomen open in severe secondary peritonitis reduces the risk of ACS, especially in patients with massive fluid resuscitation, prolonged surgery and visceral edema.

In a series of 78 patients with secondary peritonitis undergoing serial measurements of the intra-abdominal pressure (IAP), 32 (41%) developed IAH postoperatively [48].

Among the 16 patients (21%) who developed postoperative peritonitis (13 of them died), 12 had significantly elevated IAP. The authors concluded that elevated IAP postoperatively can increase the risk of postoperative peritonitis and that postoperative IAP measurement can be used to determine the need of early relaparotomy.

Obviously, the relationship between abdominal sepsis and ACS can not be studied in isolation but needs to be combined with the overall assessment of the most appropriate techniques of source control, potential benefits of deferred anastomosis (DA) and modern TAC methods such as the vacuum-assisted wound closure and mesh-mediated fascial traction (VAWCM). Perhaps it is time for a randomized study comparing standard laparotomy and ROD with OA+VAWCM+DA in severe secondary peritonitis?

## INTENSIVE CARE AND ANTIMICROBIAL THERAPY

Patients with severe IAI require admission to the ICU either pre or post sepsis control surgery. Preoperative admission may be necessary in patients who present with overt organ dysfunction such as hypotension, important metabolic disturbances, such as electrolyte disorders or acidosis.

Nevertheless, source control and antibiotic therapy remain the cornerstones of treatment in critically ill patients with abdominal infections [49]. In recent years there has been an increased focus on the appropriate use of antibiotics. Significant evidence has demonstrated that an inappropriate antibiotic spectrum and a delay in antibiotic initiation are important contributors to the morbidity and mortality of severe infections [50]. Although bundles have been introduced in various colors and flavors, the most cited key factors include appropriate sampling and timely initiation of an appropriate spectrum of antibiotics [51]. Applying these principles to abdominal infections suggests that antibiotics should be started upon diagnosis, in the emergency room or ICU, without waiting for results of abdominal exploration or percutaneous drainage. Although cultures are often considered unnecessary, it is prudent to take cultures in severely ill patients as antibiotic resistance, even in community-acquired disease, is on the rise. This is also supported by the fact that large-scale epidemiological data are lacking for most hospitals, regions and countries. Despite delays in culture results, novel methods allow for more rapid identification making faster targeted therapy feasible. Similarly, de-escalation of empiric broad-spectrum antibiotic therapy may be guided by intraoperative cultures. Anaerobic bacteria, though difficult to culture, should always be covered with initial and narrowed antibiotic therapy.

Debate continues regarding the pathogenic role of fungi and enterococci in these infections [52]. Both appear to be more frequently isolated in severe infections, and have been

inconsistently associated with adverse outcomes. There seems to be consensus that enterococci should be covered by the initial empirical scheme. Fungal coverage is recommended in cases of anastomotic leakage or when fungi are isolated from the intraoperative cultures [53].

Apart from the timing and spectrum of antibiotics, there is increasing evidence that appropriate dosing is an additional challenge for critically ill patients with abdominal infections. An increased volume of distribution, enhanced elimination from the circulation, as well as changes in protein binding (largely due to lower albumin levels) all contribute to the unpredictable pharmacokinetics of antibiotics [54]. Beta-lactam antibiotics — the mainstay of antimicrobial therapy for IAI — appear to be significantly affected. Strategies aimed at improving the pharmacokinetics/pharmacodynamics of antibiotic therapy include the use of higher doses, loading doses and extended and continuous infusion. However, even these strategies may be inadequate in some situations.

In patients with abdominal infections, the standard goals and treatments relevant for all critically ill patients apply. Particular attention should be paid to the abdominal compartment as these patients are at risk for a number of surgical complications.

The timing of source control measures is also important in the treatment of critically ill patients with abdominal infections. Generally, the presence and extent of ongoing contamination, the severity of clinical signs and symptoms, the rapidity of deterioration and the degree and dynamics of organ dysfunction determine the urgency of source control measures. Based on these concerns, three patient categories have been proposed [55]:

1. Patients requiring source control as soon as possible, with an increased risk of mortality and significant morbidity in case of delay. Examples are necrotizing fasciitis and intra-abdominal infections with deteriorating organ function or compartment syndrome. In these patients, resuscitation should not be delayed but can be accomplished simultaneously.
2. Patients requiring source control as soon as patient physiology allows. Adequate resuscitation and correction of metabolic disorders is attempted during a reasonable interval prior to intervention. Most patients with complicated intra-abdominal infections are in this category.
3. Patients who do not require source control right away. Source control is best postponed until the inflammatory process has demarcated; patients with infected pancreatic necrosis and patients with smaller abscesses that are not amenable to percutaneous drainage and would require high-risk open surgery would often be in this category.

Defining adequate resuscitation and stabilization is important in this context. Complete hemodynamic stability or complete correction of metabolic disorders is often an elusive goal. Once a patient is no longer hypotensive (albeit under treatment with vasoactive drugs), is adequately oxygenated and major coagulopathy and acidosis has been corrected, a patient can be considered fit for surgery.

Obstacles to early source control are numerous in the ICU. Despite the vast array of available tools, the diagnosis of IAI often remains particularly challenging in the ICU patient. A lack of clinical symptoms due to sedatives or pain medication is probably one of the main determinants of delayed diagnosis. This often leads to an increased number of technical investigations; although access to radiological examinations such as CT scan (or MRI — even though the latter rarely reveals more information than contrast enhanced CT scan) may often be more complex. Concomitant infections are often present and blamed for clinical deterioration. Delay in treatment on the other hand is also frequent. Interventional radiology services may not readily be available and even surgery is sometimes delayed due to logistical or staffing issues during out of office hours.

Source control no longer means surgery — as an example, interventional radiology has made considerable advances and, in pancreatitis patients, radiologic intervention may be the preferred initial method for obtaining source control [56]. This should however not minimize the benefits of surgery while in some patients a temporizing strategy may not be the optimal treatment. When selecting a source control modality, the benefits and risks for the patient at that particular moment should be carefully considered. The method that causes the least collateral damage in reaching a specific goal at a specific time is preferred. For example, percutaneous rather than surgical abscess drainage may be preferred in some situations, keeping in mind that any kind of intervention may cause bleeding and additional organ damage. Acute cholecystitis is such an example where cholecystectomy (open or laparoscopic) and cholecystostomy are both valuable alternatives and the condition of the patient will determine the optimal strategy. The intensivist, surgeon and interventional radiologist should closely cooperate, determine the goals of therapy and together determine the optimal therapeutic approach.

Equally challenging is the problem of failed source control. It significantly contributes to the morbidity and mortality of surgical procedures as it typically occurs in patients who cannot tolerate additional damage and may increase risks for other complications. The clinical setting of persistent organ dysfunction and elevated inflammatory markers in postoperative patients should rouse suspicion of failed source control. Diagnosis is notoriously difficult since clinical examination is unreliable and abdominal CT scan is

often equivocal. Some recent studies have provided more insight into this matter. A large prospective study from the Netherlands found that the following variables were not associated with failed source control on relaparotomy: the extent of peritonitis, the focus of infection or etiology, the type of contamination, nor operative variables such as the presence of a new anastomosis. Rather, clinical values such as high fever, tachycardia, low P/F ratios as well as age and hemoglobin value were associated with failed source control [57]. Procalcitonin (PCT) has also been studied in this field and an increase in postoperative PCT levels was predictive of failed source control [58].

Enteral nutritional support is important in patients with IAI for a number of reasons. It avoids the need for parenteral nutrition (PN) and has been linked to a number of improved outcomes. Enteral nutrition (EN) should be actively pursued and can be safely administered in most patients after surgery. OA management is not a contraindication to enteral nutrition.

A number of recent large studies have focused on the role of supplemental parenteral nutrition. In a general ICU population, adding PN to EN was associated with an increase in infectious complications [59]. Contrary to these findings, a Swiss group found that adding PN to EN in a select group of patients was associated with marked benefits [60]. Targets in the latter study were based on the results of indirect calorimetry. Notably, in the Belgian study, patients in whom EN was contraindicated did worse (both higher morbidity and mortality) when receiving PN compared to receiving no nutritional support [59].

These findings have further fueled the discussion as to who needs support and also how much. From a practical point of view, it appears wise to institute EN when possible, preferably using a protocol, in hemodynamically stable patients. Similarly, it is prudent to withhold EN when the patient is on a significant dose of vasopressors or whenever GI hypoperfusion is suspected. Adding PN in the first 7 days of ICU stay does not convey any benefit and should be avoided.

## TERTIARY PERITONITIS

Tertiary peritonitis can be defined as the persistence or recurrence of intra-abdominal infection after apparently adequate treatment for primary or secondary peritonitis. It is characterized by organ dysfunction and prolonged systemic inflammation in association with recurrent peritoneal infection with organisms of low intrinsic pathogenicity [61].

In a study of 59 patients with secondary peritonitis, tertiary peritonitis, defined as a culture-confirmed intra-abdominal infection persisting or recurring at least 48 hours after apparently adequate treatment of secondary bacterial peritonitis, was observed in 44 patients (74%) [61]. The most common infecting organisms identified were *Enterococcus*, *Candida*, *Staphylococcus epidermidis*, and *Enterobacter spp.* Infectious foci were rarely amenable to percutaneous drainage and were found to be

poorly localized at laparotomy. Compared with patients with uncomplicated secondary peritonitis, tertiary peritonitis was associated with higher ICU mortality (64% vs. 33%), higher organ dysfunction scores and ICU length of stay.

More recent studies have grouped tertiary peritonitis among “complicated” intra-abdominal infections. These include persisting peritonitis despite adequate surgical and initial antimicrobial therapy [62], “persistent and tertiary chronic” peritonitis with distinct changes in immunoresponsiveness [63], and where there has been a prolonged course with microbiological shift from aerobic gram-negative bacteria towards gram-positive bacteria over time [64]. In a study of 69 patients with secondary peritonitis among whom 15 patients (22%) developed tertiary peritonitis, transition to tertiary peritonitis was associated with a higher Mannheim Peritonitis Index at the initial operation, higher severity of illness scores and CRP levels on the second postoperative day, higher relaparotomy rates with increased mortality (60% vs. 9%), and a longer ICU length of stay [65].

Specifically, *Candida* peritonitis seems to be increasing in incidence and continuing to be associated with high mortality. Factors that have been identified with increasing risk of development of *Candida* peritonitis include hollow viscus perforation, abdominal and thoracic surgery, surgical drains *in situ*, intravenous and urinary catheters, total parenteral nutrition, severe sepsis, antibiotic therapy more than 48 hours before peritonitis, immunosuppression, diabetes mellitus and extensive *Candida* colonization [66].

In future, tertiary peritonitis needs to be defined more clearly, perhaps utilizing some immunological markers. Furthermore, it would be interesting to see whether staged repair in severe secondary peritonitis would be associated with a lower risk of tertiary peritonitis.

## CONCLUSIONS

Timely surgical or non-surgical source controlling intervention geared to the pathophysiological state of the patient, the appropriate use of antimicrobial agents and early intensive care offer the best chance of survival for patients with abdominal sepsis. The essential goal of surgical intervention is controlling the source of contamination. First demonstrated in major trauma patients, the introduction of damage control to the management of secondary peritonitis represents a paradigm shift. Although limited and repeated surgical interventions have been shown to be safe, the actual benefits need to be demonstrated in controlled studies.

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**Corresponding author:**

Ari Leppäniemi, MD  
Meilahti Hospital, Abdominal Center  
University of Helsinki  
Haartmaninkatu 4  
PO Box 340, 00029 HUS, Finland  
Email: ari.leppaniemi@hus.fi

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