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Clinical controversies in abdominal sepsis. Insights for critical care settings

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ABSTRACT

Sepsis is a deadly condition in which the outcome is associated with prompt and adequate recognition, intensive supportive care, antibiotic administration and source control. This last item makes abdominal sepsis a unique treatment challenge. Although pneumonia constitutes the leading cause of sepsis, abdominal sepsis has unique features that merit discussion. The abdomen may be implicated as the primary occult, secondary dependent or secondary independent source of infection. The major factors determining whether a patient will develop an uncomplicated infection or septic shock are: (1) patient susceptibility to infections, (2) age, and (3) comorbidities. The epidemiology of abdominal sepsis and its outcomes are difficult to assess due to the large clinical heterogeneity associated with this entity. Further complicating issues is the debate surrounding the effect of early source control (*i.e.* the "surgeon effect"). This review evaluates and summarizes the current approach to current challenges in patient care and which are the future research directions.

1. Introduction

Sepsis is a silent killer [1]. It is unpredictable, rapid and often undiagnosed due to its non-specific signs and symptoms [2]. Apart from prompt recognition, survival from sepsis is associated with adequate source control and initiation of treatment with antibiotics [3]. The most common locations of the primary infection include the lungs, urinary tract, skin, and abdominal organs [4]. Although pneumonia constitutes the leading cause of sepsis, abdominal sepsis has unique features that merit discussion [5].

The abdomen may be implicated as the primary occult, secondary-dependent or secondary-independent source of sepsis [6]. Examples of each condition are displayed in Table 1. The major factors determining whether a patient will develop an uncomplicated infection or septic shock are: patient susceptibility to infections, age and comorbidities [7].

Sepsis is caused by a dysregulated host response to infection [2]. Although sepsis is a systemic process, the pathophysiological response differs between organs [8]. Initially, the inflammatory response is compartmentalized in the peritoneal cavity [9]. With disease evolution and progression to more severe and uncontrolled forms of sepsis such as septic shock and multi-organ failure, the response becomes systemic and mortality increases.

Abdominal sepsis is often polymicrobial [10,11]. Gram positive and negative bacteria share a common mechanism, which allows them to crosslink, and bind to human vascular endothelial cells. This process causes dysregulation of normal endothelial haemostasis, characterised by a loss of cell barrier integrity, apoptosis, sustained release of inflammatory cytokines and thrombus formation [12,13]. In abdominal sepsis,

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Table 1
Conditions and definitions associated to source of sepsis in critically ill patients.

Conditions	Definitions	Example
• Primary occult	• In-apparent source of the problem where the abdomen is implicated as the primary source	• Cholecystitis (calculous or acalculous) • Pancreatitis • Typhlitis • Diverticulitis & Appendicitis • Retroperitoneal abscess • Bowel ischemia with faecal peritonitis
• Secondary dependent	• When the initial process began in the abdomen	• Post operative abscess • Anastomotic leak
• Secondary independent source of sepsis	• When intra-abdominal organ sustain an insult from splanchnic hypoperfusion	• Intestinal ischemia resulting from splanchnic hypoperfusion

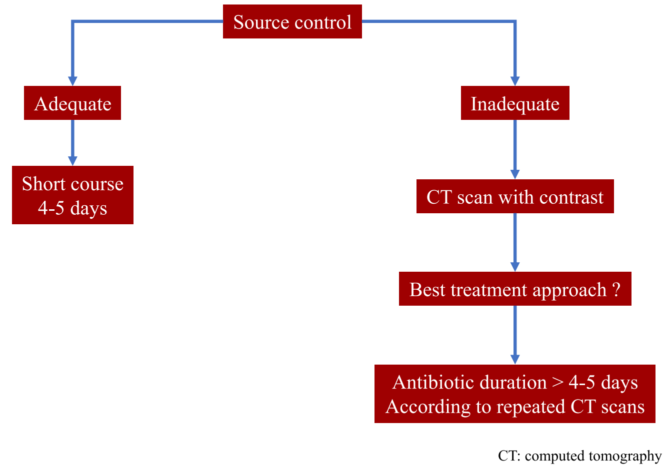

Fig. 1. Approach to source control management.

an additional concept related to vascular permeability can be considered as a mechanism of injury (*i.e.* increased vascular permeability). This mechanism is widely recognized and accepted in the lungs and kidneys, where it is classified as acute lung and kidney injury. A similar process occurs in the gut, although this concept is much slower to seep through. However, the role of the gut as the motor of organ dysfunction syndrome cannot be denied and difficulties in assessing gut function should not deter us from recognizing its driving role in the multiple organ failure [14].

The epidemiology of abdominal sepsis and its outcomes are difficult to assess due to the large clinical heterogeneity associated with this entity. Further complicating issues is the debate surrounding the effect of early source control (*i.e.* the "surgeon effect"). A recent randomized clinical trial (RCT) considered complicated intra-abdominal infections (cIAIs) in patients with mortality ranging from 2% to 3% whilst septic shock mortality rates in intensive care unit (ICU) patients can be as high as 50% [15,16].

This narrative review aims to focus in five topics of current controversy in abdominal sepsis with a focus on critically care patients. Our aim is to evaluate and summarize the current approach to common challenges in patient care and which are the future research directions.

2. Short-courses of antibiotics in patients with cIAIs

2.1. Background

CIAIs are a heterogeneous group of infections with a highly variable prognosis. The mainstay of treatment, at least for secondary peritonitis, is source control. This usually requires drainage of discrete collections and correction of the anatomic defect responsible for on-going contamination. In most cases this can be accomplished using percutaneous techniques. However, decisions regarding the type of intervention required hinges on understanding the surgical options and their risks, which requires close collaboration with a surgeon (Fig. 1).

Antibiotic therapy is an adjuvant to source control. Based on good quality evidence [17], the revised guidelines on management of cIAIs [6] recommend that antibiotic therapy be administered for an uninterrupted period of 4-7 days. The daily bedside conflict consists of the desire to eradicate the infectious process *vs.* the collective imperative to reduce antibiotic exposure in order to prevent emergence of multidrug-resistant bacteria. Unfortunately, existing guidelines have failed to show the relevance of existing RCTs for critically ill patients [18].

2.2. Literature review

The STOP-IT trial enrolled 518 patients with cIAIs and adequate source control to receive antibiotics either until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or a fixed course of antibiotics (experimental group) for 4 ± 1 calendar days [17]. The crude mortality was around 1%. The primary outcome (a composite score including surgical site infection, recurrent cIAI, or death) was similar in both groups (22.3% *vs.* 21.8%, $p = .92$). The period of exposure to antibiotics was reduced in the experimental group. While interesting, it remains uncertain whether these results may be extrapolated to critically ill patients. Ancillary studies have focused on patients with sepsis, patients at risk of complications, patients older than 64 years, and patients in whom *Enterococcus* and *Candida* were isolated [16,19-21]. These studies suggest that a 4-day course can be used in those subpopulations. However, whether these patients were truly critically ill is unclear; the features of the populations described in these studies suggest that only few critically ill patients were included.

Contrary to these studies Montravers et al. focused specifically on ICU patients receiving appropriate empirical antibiotics and an adequate source control procedure [22]. Among 410 eligible patients, 120 and 116 patients were randomized to 8-days or 15-days of antibiotic therapy, respectively. Eight days of treatment yielded a greater number of antibiotic free-days (the primary outcome) and similar 45-day mortality to 15 days of treatment, although the study was not powered for this secondary outcome. However, higher rates of percutaneous drainage and bacteraemia were observed with 8 days of treatment and the rate of multidrug-resistant bacteria emergence was similar in both groups.

2.3. Recommendations

If source control is readily achieved, short courses of antibiotics are acceptable since the focus of bacterial dissemination has been eliminated. The standard of care for most patients should probably be 4–5 days of antibiotic therapy. In a selected group of patients (*i.e.* following drainage of cholangitis), 24 h of antibiotic therapy may be suggested. Prolonging antibiotic treatment should never be an alternative to source control. Ongoing organ dysfunction despite appropriate therapy should prompt a search for a correctable cause. A computed tomography (CT) scan is the best tool for investigation as it may offer insight to the optimal treatment approach. Extending antibiotic therapy beyond 5–7 days is reasonable when despite optimal efforts, source control remains inadequate or uncertain.

2.4. Future research agenda steps

A comparison of a fixed to an individually tailored approach (based on daily clinical assessment and CT scan examination) duration of antibiotic therapy would provide important insight into the best mode of care.

3. Abdominal closure in abdominal sepsis

3.1. Background

Open abdomen treatment (OAT) refers to the action to leave the abdomen open post-surgery [23]. The precise impact of OAT in critically ill patients remains unstudied. Therefore caution should be always exercised with regards to this invasive intervention [24]. OAT was initially described for patients with severe abdominal trauma in the context of damage control surgery but has since been extrapolated to patients with cIAIs unrelated to trauma. In patients with CIAI an OAT approach may be required in several circumstances. These include 1) Rapid patient deterioration with severe physiological compromise (*i.e.* the need to shorten the length of surgery), 2) Multiple re-explorations due to ongoing infection, 3) A high likelihood of abdominal compartment syndrome and 4) An increased risk of dehiscence due to severe infection (*i.e.* the need to defer intestinal anastomosis to the post-resuscitation period). Although OAT may be lifesaving, it remains a clinical challenge because of its association with significant complications [25].

The goal of OAT in patients with cIAIs is early source control. The initial surgical intervention should therefore be kept as simple and brief as possible. After source control, the patient should be admitted immediately to the ICU for physiologic optimization. Once physiological balance has been achieved, the patient may be returned to the operating room for a definitive operation. This usually occurs within 24–48 h. Re-exploration and definitive surgery should ideally be accompanied by definitive closure of the abdomen as this constitutes the basis for preventing or reducing complications [26]. In a 2014 meta-analysis, Chen et al. showed clinical advantages of early fascial closure over delayed approach in treatment of patients with open abdomen [27].

3.2. Literature review

The literature suggests there is a bimodal distribution of primary closure rates, with early closure within 7 days and delayed closure after 7 days. These are mostly determined by the technique used for temporary abdominal closure [28]. Primary closure of the fascia can be achieved in many cases within days of the initial operation without technical difficulties. Although patients with abdominal sepsis are less likely to undergo early fascia closure [29], this should be attempted as soon as sepsis is controlled [27] in order to reduce complications.

The most serious local complication in patients with OAT is development of an entero-atmospheric fistula. The exposed bowel is at risk of fistulization especially in patients with longstanding OAT. Spontaneous closure of such fistulae is very rare as the overlying tissue is poorly vascularized [30]. Delayed fascial closure is defined as fascial abdominal closure 7 or more days after the opening of the abdomen. Delayed facial closure is best achieved by progressively and incrementally approximating the edges of the fascia edges until the abdominal wall defect has been completely closed.

Temporary abdominal closure should optimally protect the abdominal contents, prevent evisceration, allow removal of infected or toxic fluid from the peritoneal cavity and prevent formation of fistulas. It should also avoid damage to the fascia, preserve the abdominal wall domain, make re-operation easy and safe and facilitate definitive closure. Negative pressure wound therapy techniques are now extensively used for temporary abdominal closure. This method actively exhibits species selectivity, suppressing the proliferation of nonfermenting gram-negative bacilli [31], allowing fascial and abdominal wall closure [32]. Occasionally, abdominal closure cannot be achieved. Such cases are prone to late development of large abdominal hernias, which may require complex surgical repair [33].

3.3. Recommendations

OAT may be lifesaving but its association with significant morbidity poses unique clinical challenges. Current guidelines suggest avoiding routine OAT for patients with cIAIs, but this approach is a pertinent clinical option in a select group of patients with severe physiologically derangement and ongoing infection [6]. In addition, intraabdominal pressure (IAP) should be continued during OAT as it can guide closure. It should be realised that patients with OAT can still develop ACS; IAP can reliably be measured when a vacuum assisted closure (VAC) dressing is applied. It is not advocated to primarily close abdomen when there is still grade 2 or higher intrabdominal hypertension (IAH). An integral approach should be also taken into account with an optimal fluid management to optimize “peritoneal resuscitation” on one hand and in order to avoid developing acute bowel injury and acute intestinal distress syndrome on the other [34–36]. Adequate nutrition support is critical in the management of patients with an open abdomen [37]. Several formulas can be used but as a general rule, an estimate of 2 g of nitrogen per litre of abdominal fluid output has been proposed/suggested when calculating the nitrogen balance of any patient with an open abdomen [38]. There are several important surgical considerations, such as avoiding exposed feeding tubes, use of permanent meshes in the abdominal wall. If necessary, the use of a non-adherent visceral layer might be preferable [39].

If a decision has been made to manage the patient with an OAT, reducing the rate of associated complications by early primary closure of the fascia is recommended once the source of sepsis has been controlled. Negative pressure wound therapy should be considered for temporary abdominal wall closure as it offers several advantages. It is clear that when opening the abdomen and leaving it open one should think immediately about when to close [40]. “*If you fail to plan, you plan to fail*” accurately summarizes the main goal in this situation: begin planning closure as soon as the abdomen is opened [41].

3.4. Future research agenda step

Although strong evidence is lacking, there is a clinical feeling that in some cases with cIAI opening the abdomen may promote resolution of the infectious process. Retrospective studies report on use of OAT in patients with cIAIs. However, only one study reported randomization of patients to a closed or open strategy in recent years [42]. Using a sandwich technique with non-absorbable mesh sutured to the fascia performed the temporary abdominal closure. This study was stopped at the first interim analysis because the risk of death was higher in the OAT group although not reaching statistical significance. Another study [43] is now planned to address this question in the most severe patients (NCT03163095).

Because in cIAIs several laparotomies may be required, two types of well-designed studies comparing two approaches are required in this population: 1) OAT with temporary abdominal closure compared to primary abdominal closure with on-demand laparotomy; 2) Primarily closure of the fascia *vs.* leaving the fascia open and applying a temporary abdominal closure device with a vacuum drain.

4. Timing of source control

4.1. Background

Source control is pivotal in the management of cIAIs. Drainage of the infection, thereby controlling the ongoing contamination is considered crucial to patient outcome. The methods used to obtain source control

Table 2
Source control timing.

Authors ref	Type of patients (number)	Type of study	Main result
Coccolini et al. [15]	Intraabdominal infections secondary to complicated diverticulis ($n = 272$)	Ancillary assessment from 2 multicenter prospective observational studies	Increased mortality after 24 h
Karvellas et al. [16]	cholangitis-associated septic shock ($n = 260$)	Retrospectvie, observational	Endoscopic biliary decompression >12 h after the onset of shock and delayed receipt of appropriate anti-microbial therapy both associated with adverse hospital outcome
Boyer et al. [19]	Necrotizing soft tissue infections ($n = 106$)	Retrospective, observational	Time from diagnosis to surgical treatment >14 h in patients with septic shock independently associated with hospital mortality
Vergidis et al. [20]	Intraabdominal candidiasis ($n = 163$)	Retrospective, observational	Early interventions (within 5 days of collecting the first culture-positive sample for *Candida*) associated with survival
Solomkin et al. [21]	Intraabdominal infection	Systematic analysis of literature of prospective randomized clinical trials ($n = 8$)	Definition of successful source control using percutaneous catheter drainage: include a reasonable time limit (achieved within 4 days)
Abou-Nukta et al. [22]	Delaying appendectomy for 12 h	Retrospective, observational ($n = 309$)	Delaying appendectomies for acute appendicitis for 12 to 24 h after presentation: no significant increase the rate of perforations, operative time, or length of stay

may be surgical (laparotomy or laparoscopy), or non-surgical (percutaneous drainage). The method selected should be determined by local capabilities, the presumed source and extent of infection, the surgical history and patient physiology. The optimal timing of source control remains a controversial topic. The Surviving Sepsis Campaign Guidelines 2016 recommend controlling the source of infection as soon as logistically and medically practical after diagnosis is made, and no longer than 6–12 h after diagnosis [44], but it is unclear if earlier intervention is beneficial. This question is important; access to emergency abdominal surgery or interventional radiology 24/7 places a significant burden on hospital staff and resources. Of course all available data suffer from the lack of accurate definition of adequacy of the initial surgical procedure to the management of the infection [45].

4.2. Literature review

To date, the data addressing the timing of source control intervention is limited to observational studies, which may introduce significant bias to current knowledge. These studies are also confounded by data from heterogeneous populations (*e.g.* different sources of sepsis) and lack of adjustment for other important determinants of outcome (*e.g.* adequacy of antibiotic therapy, efficacy of resuscitation). They are also often limited by focus on specific types of cIAIs. Furthermore, many studies use cut-offs (*e.g.* 6, 12 or 24 h) rather than assessing the time to source control as a continuous variable.

Despite existing recommendations, current literature shows that source control is not a priority at times. A Spanish study reported a median of 4.6 h between the onset of severe sepsis or septic shock and source control [46] and a German study reported a 2 h median interval between the diagnosis sepsis and source control [47]. However, a study from the UK reported that the median times to source control were 18 and 24 h in patients with severe sepsis and septic shock respectively [48].

Inadequate or delayed or source control is an independent predictor of poor outcomes and recognizing "failed source control" is often difficult or impossible without abdominal re-exploration [49]. In patients with diverticulitis, Coccolini et al. found increased mortality if the initial intervention was delayed beyond 24 h [50]. In septic shock from biliary origin, delayed biliary decompression beyond 12 h led to worse outcome [51]. But does further shortening the interval to surgery provide any benefit? In patients with peptic ulcer perforation, each hour of delay between admission and surgery was associated with a 2.4% increase in mortality. In a Japanese study in patients with septic shock due to gastrointestinal perforation, each hour of delay was associated with a steep increase in mortality [52]. Bloos et al. found in a large multicentre study that mortality increased by 1% per each hour of delay in source control [47]. Earlier smaller-scale data from the same group did not show this finding [53].

4.3. Recommendations

The current evidence suggests there is no reason to delay source control even for a few hours in most patients with cIAI. Source control interventions in these vulnerable patients should be done with care. The type of intervention and physician expertise should be matched to the severity of the disease and complexity of the procedure. A careful evaluation of patient condition and their test results (including imaging) should precede the decision regarding the choice of source control intervention. The one exception to this rule is infected pancreatic necrosis, where a conservative strategy of waiting until the infectious focus is well-demarcated and amenable to drainage is preferred [54].

4.4. Future research agenda steps

Given the lack of robust information in patients with cIAIs, large scale observational studies could provide some insight to the impact of source control timing. RCTs on this topic are challenging to organize and may be considered unethical. When evaluating the timing of source control, adjustment should be made for additional characteristics that may affect outcome (*e.g* the method of source control and its adequacy). A panel of intensivists, surgeons and interventional radiologists should ideally review the adequacy of the source control intervention. Studies should also include information regarding the time of hospital admission, of diagnosis of cIAI, and of sepsis onset (Table 2).

5. Conclusion

Sepsis is a deadly condition in which the outcome is associated with prompt and adequate recognition, intensive supportive care, antibiotic administration and source control. This last item makes abdominal sepsis a unique treatment challenge. This review summarised the current approaches and dilemmas regarding five of the more common challenges in critically ill patients affected by abdominal sepsis.

COI

No COI to declare regarding the content of this manuscript by any of the authors.

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