

Hot Topics in Acute Care Surgery and Trauma

Massimo Sartelli

Matteo Bassetti

Ignacio Martin-Loeches *Editors*

# Abdominal Sepsis

A Multidisciplinary Approach



WORLD SOCIETY OF  
EMERGENCY SURGERY



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# Hot Topics in Acute Care Surgery and Trauma

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Massimo Sartelli • Matteo Bassetti  
Ignacio Martin-Loeches  
Editors

# Abdominal Sepsis

A Multidisciplinary Approach

 Springer

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## Foreword

Since 2011, the founding members of the World Society of Emergency Surgery (WSES) Acute Care and Trauma Surgeons group, in collaboration with the American Association for the Surgery of Trauma (AAST), endorse the development and publication of the “Hot Topics in Acute Care Surgery and Trauma,” realizing the need to provide more educational tools for young in-training surgeons and for general physicians and other surgical specialists. These new forthcoming titles have been selected and prepared with this philosophy in mind. The books will cover the basics of pathophysiology and clinical management, framed with the reference that recent advances in the science of resuscitation, surgery, and critical care medicine have the potential to profoundly alter the epidemiology and subsequent outcomes of severe surgical illnesses and trauma. In particular, *abdominal sepsis* requires detailed understanding as the population ages presenting with multiple co-morbidities. The challenge of dealing with often elderly and sicker patients is potentially balanced however by newer less invasive surgical techniques and advances in peri-operative critical care, demanding careful judgement in applying the right therapies to the right patients.

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## Preface

Intra-abdominal infections (IAIs) are an important cause of morbidity and mortality. Management of IAIs requires a multidisciplinary approach. The treatment of patients with complicated intra-abdominal infections (cIAIs) involves both source control and antimicrobial therapy. However, while surgical techniques improved treatment modalities for these patients, the adequate use of antibiotics within the management of cIAIs plays an integral role to prevent local and hematogenous spread and to reduce late complications. The choice of empiric antibiotics in patients with IAI should be based on the severity of the infection, the individual risk for infection by resistant pathogens, and the local resistance profile. Predisposing conditions, the nature and extent of insult, the nature and magnitude of the host response, and the degree of concomitant organ dysfunction provide a useful and novel approach to IAIs. In this book, experts from different fields in the management of severely ill patients affected by IAIs contributed to give a broad and multidisciplinary approach to the management of IAIs.

The first chapters of the book describe the difficulties related to classification, diagnosis, the radiological caveats, and challenges in patients affected by IAIs. This part is followed by a series of chapters that focus on the difficulties of source control, the alternatives in management, and the new developments of damage control surgery. In the last chapters, the most severe spectrum of the disease is discussed, with a focus on antibiotic management, including antifungals, hemodynamic support, and alternatives to adjunctive therapies in the pipeline.

When the book was conceived, our aim was to provide a broader approach to IAIs, and this is the reason why, as said above, we decided to involve the most renowned experts from three different disciplines: surgery infectious diseases, and intensive care. We hope that this might help to integrate the information already available to the readers, widening the perspective on this topic.

Macerata, Italy  
Udine, Italy  
Dublin, Ireland

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Matteo Bassetti  
Ignacio Martin-Loeches

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# Classification and Principals of Treatment

1

Amelia Simpson, Leslie Kobayashi, and Raul Coimbra

## 1.1 Introduction

Intra-abdominal infection (IAI) is the second most common cause of severe sepsis in the intensive care unit (ICU). Even with optimal care, this disease process confers significant morbidity and mortality. The most common causes of IAI involve inflammation and perforation of the gastrointestinal tract including appendicitis, diverticulitis, and peptic ulcer disease. Other etiologies often more challenging to treat include postoperative complications, iatrogenic procedural complications, and traumatic injuries. Treatment is multimodal including, most importantly, source control in conjunction with timely systemic antimicrobial therapy, resuscitation, and supportive care. Given the wide spectrum of disease from focal isolated inflammation to diffuse peritonitis with septic shock and organ failure, the treatment is varied and complex. This chapter includes a review of clinical definitions and classification of the disease process as well as a basic overview of treatment.

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## 1.2 Classification

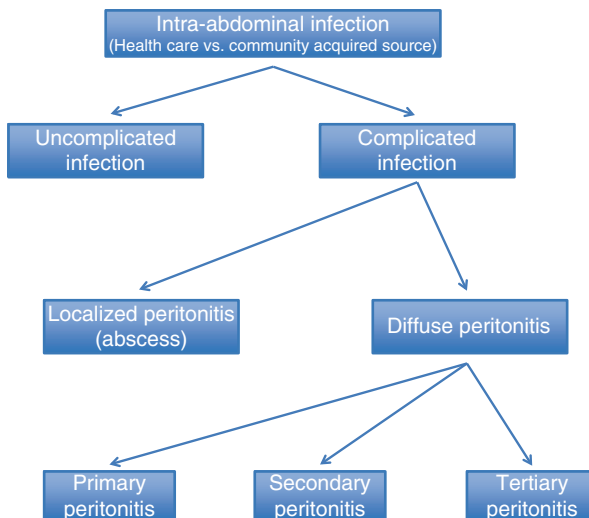
### 1.2.1 Intra-abdominal Infections

IAI is the inflammatory response of the peritoneum to microorganisms and their toxins which produces purulence within the abdomen [1]. These intra-abdominal infections are classified as uncomplicated or complicated based on the extent of infection within the abdominal cavity (Fig. 1.1).

An uncomplicated IAI is confined to a single organ. There is intramural inflammation of the organ, but no perforation. These infections are generally simple to treat with surgical source control; however, delay in diagnosis, delay in definitive treatment, or infection with a virulent or nosocomial microbe can result in advancement to a complicated IAI [2-4].

Complicated IAIs spread beyond the causal organ when the viscus perforates into the peritoneal cavity. Peritoneal inflammation occurs causing localized or diffuse peritonitis and greater activation of the systemic inflammatory response system [3, 5]. Localized peritonitis is often a result of a contained infection or abscess. Diffuse peritonitis is associated with higher morbidity and mortality and requires urgent surgical treatment. Diffuse peritonitis is divided into primary, secondary, and tertiary forms.

Most intra-abdominal infections activate the inflammatory cascade; however, an IAI which causes severe sepsis or septic shock is described as abdominal sepsis [3].



**Fig. 1.1** Classification of intra-abdominal infections

## 1.2.2 Peritonitis

### 1.2.2.1 Primary Peritonitis

Primary peritonitis also known as spontaneous bacterial peritonitis is the result of bacterial translocation across the GI tract in the absence of any discrete visceral defect. Bacterial translocation occurs via multiple proposed mechanisms including alterations in the local immune defense, intestinal bacterial overgrowth, and impairment in the intestinal barrier [6, 7]. These infections are frequently caused by a single organism and afflict specific patient populations. Commonly cirrhotic patients are infected with gram-negative or *Enterococci* organisms, peritoneal dialysis patients with *Staphylococcus aureus*, and young females with *Pneumococcus* species [8, 9]. Physical findings may be subtle. The diagnosis is made by peritoneal fluid aspirate. Peritoneal fluid will show  $>500$  white blood cells/mm<sup>3</sup>, increased lactate, and/or low glucose. Positive fluid cultures are diagnostic. Resolution is indicated by a decrease in the peritoneal white blood cell count to  $<250$ /mm<sup>3</sup> [10]. Primary peritonitis is treated with systemic antibiotics tailored to the offending organism [11]. Outcome is generally good following appropriate therapy; however, mortality is increased among patients requiring admission to the intensive care unit [12].

### 1.2.2.2 Secondary Peritonitis

Secondary peritonitis is caused by direct peritoneal contamination from the GI tract due to perforation, injury, or necrosis [8, 13]. Etiologies include acute perforation, specifically perforated appendicitis, perforated ulcers, diverticular disease, volvulus, cancer, or small bowel obstruction. Additional causes include postoperative complications such as anastomotic dehiscence and traumatic blunt or penetrating injuries [14]. Diagnosis of secondary peritonitis is mostly based on history and clinical examination. Specific diagnoses can be confirmed with diagnostic imaging, most often computed tomography (CT) and ultrasound [15]. Ultrasonography is a particularly useful initial imaging for the diagnosis of biliary sources of peritonitis; however, CT of the abdomen and pelvis with intravenous and oral contrast is the standard imaging modality to diagnose intra-abdominal causes of peritonitis [16]. It must be kept in mind that only patients who are well resuscitated and hemodynamically stable should undergo CT scanning. Secondary peritonitis is generally polymicrobial with the causal organisms correlating to the source of contamination.

### 1.2.2.3 Tertiary Peritonitis

The International Sepsis Forum Consensus defines tertiary peritonitis as peritonitis which persists or recurs  $>48$  h following apparently successful management of primary or secondary peritonitis [17]. This is thought to be due to altered microbial flora, failure of immune response, or progressive organ dysfunction. Patient age, malnutrition, and the presence of multidrug-resistant organisms may be risk factors for developing tertiary peritonitis. A microbial shift occurs in these patients toward less virulent organisms such as *Enterococcus*, *Enterobacter*, *Staphylococcus epidermidis*, and *Candida* [18–20].

An additional critically important distinction in this disease process is differentiating community-acquired IAIs from hospital acquired IAIs. Community-acquired infections are sensitive to narrow-spectrum antimicrobial agents. Hospital-acquired cases develop in hospitalized patients, residents of long-term care facilities, or patients who have recently been treated with antibiotics. All postoperative IAIs are therefore hospital-acquired intra-abdominal infections. Not surprisingly, hospital-acquired IAIs are associated with increased mortality [21].

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### 1.3 Prognostic Evaluation

Early prognostication of patients with IAIs is crucial to assess severity and decide on the aggressiveness of treatment. Numerous factors affecting the prognosis of patients with complicated IAIs have been described including advanced age, poor nutritional status, preexisting comorbid conditions, immunosuppression, presence of abdominal sepsis, poor source control, end-organ failure, prolonged hospitalization, and infection with nosocomial organisms [22–26]. Stratification of the patient’s risk is paramount in order to optimize the treatment plan. Patients are generally categorized as low risk or high risk. High risk describes patients who are at high risk for treatment failure and mortality; therefore, early prognostic evaluation is critical to appropriately treat the high-risk patients aggressively [27]. There are several scoring systems used to stratify patients. There are disease-independent scores for evaluation of patients requiring the intensive care unit admission such as APACHE II and Simplified Acute Physiology Score (SAPS II). There are also peritonitis-specific scores such as Mannheim Peritonitis Index (MPI). More recently, the WSES Sepsis Severity Score is a new scoring system for complicated IAIs that considers infection-related factors and patient clinical characteristics and is easy to calculate [27].

---

### 1.4 Treatment

The key components of the treatment of abdominal sepsis include source control, resuscitation and organ support, and systemic antibiotic therapy. The most critical component is source control [28]. Minimizing time from presentation to diagnosis and treatment significantly reduces morbidity and mortality [29].

#### 1.4.1 Source Control

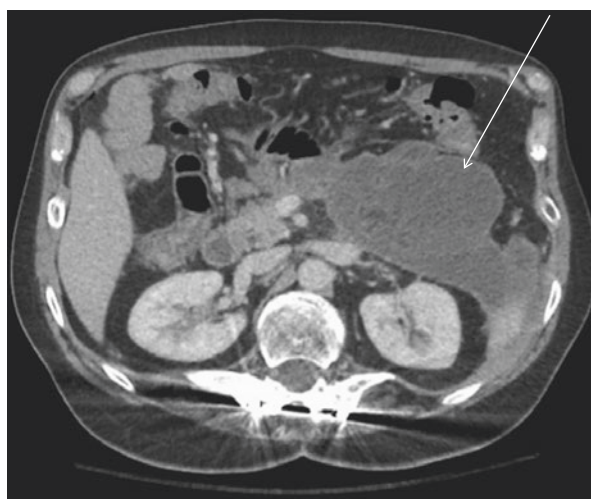
Source control is defined as the physical eradication of a focus of infection as well as modifying any risk factors that maintain infection such as ongoing spillage or leakage of enteric contents. Inadequate source control at the time of initial treatment is associated with increased mortality in patients with IAIs despite optimal antibiotic therapy, resuscitation, and organ support [30].

### 1.4.1.1 Drainage

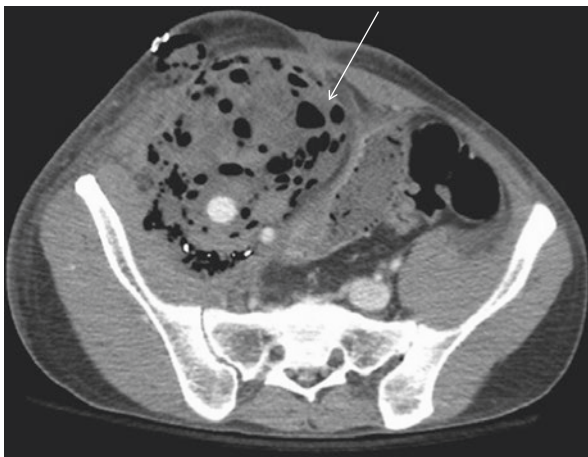
The goal of drainage is to evacuate purulent fluid or to control ongoing contamination. This can be performed in a percutaneous or open surgical manner. Percutaneous drainage is less invasive, less expensive, and ideal for contained abscesses or fluid pockets. It is most commonly performed with ultrasound or CT guidance [31, 32]. This technique is also useful for poor surgical candidates who would not tolerate the stress of an operation (Fig. 1.2).

Complex abscesses with enteric connection should be drained operatively [33] (Fig. 1.3). Surgical drainage should also be used to treat complex generalized peritonitis, ongoing enteric contamination, if necrotic or ischemic bowel is suspected or if percutaneous drainage has failed. Depending on the clinical situation and surgeon experience, this can be safely done in a laparoscopic or open manner [34]. Debridement of necrotic tissue and removal of fecal matter, gross contamination, hematoma, and foreign bodies are critical for adequate source control. Removal of fibrin deposits has been described, however has been shown to have no benefit, and is therefore not generally performed [35].

Intra-abdominal lavage is a debated technique for treatment of peritonitis. Advocates of peritoneal lavage argue that the technique improves outcomes in four ways. First, the solution acts as a physical cleanser by washing away contamination, bacteria, blood, and bile. Second, using lavage volumes greater than 10 L has a dilutional effect on contamination and bacteria. Third when antimicrobial agents are added to the lavage solution, specific offending microbes can be targeted. Lastly, use of a hypotonic solution will result in tumor and bacterial cell lysis [36]. Unfortunately the use of this technique for treatment of abdominal sepsis is largely unsupported by the literature as most recent studies have not shown any benefit from peritoneal lavage with or without the addition of antibiotics [37, 38].



**Fig. 1.2** A CT image of an intra-abdominal abscess (*arrow*) amenable to percutaneous drainage



**Fig. 1.3** A CT image of a complex intra-abdominal fluid collection with free air (*arrow*) and fecal contamination requiring surgical exploration

#### **1.4.1.2 Damage Control Laparotomy**

Clinically unstable patients or those with difficult or complicated anatomy such as postoperative patients and those with advanced malignancies or with intra-abdominal hypertension (IAH) are particularly problematic to treat surgically. In these situations a staged approach or damage control techniques can be useful with the use of a temporary abdominal closure. The concept of damage control laparotomy (DCL) first began in trauma patients and has since spread to the general and vascular surgery realms. Damage control principles are now widely adopted in abdominal surgical emergencies where primary closure is not advisable [39]. The DCL technique has three stages. The first stage is an abbreviated initial procedure aimed at controlling contamination; removal of infected, necrotic, or ischemic tissue; and hemorrhage control. If needed because of instability or questionable tissue viability, the bowel can be left in discontinuity. This initial procedure is concluded with a temporary abdominal closure (TAC). The TAC should prevent evisceration, evacuate fluid, allow quick access to the abdomen, and allow for abdominal swelling [40, 41]. The second stage of DCL is resuscitation aimed at restoring normal physiology. Once this is achieved and concerns for ongoing ischemia, necrosis, and IAH are resolved, the patient is taken back to the operating room for the third stage which is definitive source control, reconstruction, and abdominal wall closure [42].

#### **1.4.1.3 Planned Relaparotomy Versus On-Demand Relaparotomy**

There are two accepted strategies for relaparotomy. First is a planned relaparotomy. The second is on-demand relaparotomy performed only when the patient's condition demand it. Planned relaparotomy is performed every 36–48 h for evaluation, drainage, and lavage until resolution of ongoing peritonitis. This strategy can lead to early detection of ongoing peritonitis or new infection with the goal of preventing



ongoing sepsis and development of multiorgan failure. Unfortunately this can lead to unnecessary laparotomies without improvement in outcomes. The on-demand laparotomy strategy is intended to perform repeat laparotomy only on patients who clinically would benefit from surgery. Specifically those who require on-demand laparotomy are patients with clinical deterioration or lack of improvement after initial laparotomy. This treatment strategy requires close monitoring of patients with clinical criteria, laboratory studies, and imaging to efficiently identify patients who require relaparotomy. It also allows for less invasive percutaneous image-guided interventions to address ongoing infections or abscesses instead of a planned relaparotomy. This strategy harbors risk of potentially harmful delay in the detection of ongoing peritonitis [43]. The goal of on-demand laparotomy is to identify patients at risk for persistent intra-abdominal sepsis and intervene before developing multiorgan failure. Studies have shown significant cost savings and shorter ICU and hospital stay and number of days on the ventilator with the on-demand laparotomy strategy compared with planned re-laparotomy [44, 45]. Studies have not shown a difference in mortality between the two strategies, and specific clinical criteria are still needed to improve the accuracy of identifying patients requiring on-demand laparotomy [45–47].

#### 1.4.1.4 Definitive Management

Definitive management involves restoration of function and anatomy. Staged procedures with temporary intestinal diversion were once standard; however, in the stable, physiologically normal patient, single-stage procedures can be safely performed and are cost-effective [48]. Nevertheless, in patients who will not tolerate longer procedures and have poor tissue healing capacity or little physiologic reserve, staged procedures with enteric diversion are still the preferred operative choice [4].

### 1.4.2 Resuscitation and Organ Support

Intra-abdominal infections result in volume depletion both from significant insensible losses and third spacing of fluid from sepsis-driven capillary leak. As with many infectious processes, fever results in fluid loss from diaphoresis, and tachypnea increases respiratory losses. Common symptoms of IAIs include nausea, vomiting, and decreased oral intake which all lead to dehydration and further fluid losses. Bowel wall edema and ascites can occur from the IAI associated ileus and inflammatory process. The systemic inflammatory response cascade will cause further volume depletion due to capillary leak and third spacing of fluid. Expedient volume resuscitation is therefore critical in the treatment of IAIs and abdominal sepsis. Any patient with severe sepsis or septic shock should be admitted to the intensive care unit for close monitoring of hemodynamics and volume status. The first 6 h of resuscitation should be performed following the Surviving Sepsis Campaign Guidelines. Isotonic fluid should be used for volume resuscitation or blood products in the setting of anemia or coagulopathy to achieve a goal central venous pressure (CVP) of 8–12 mmHg, mean arterial pressure (MAP) of >65 mmHg,

goal urine output of  $>0.5$  mL/kg/h, and central venous or mixed venous oxygen saturation of 70% or 65%, respectively [49]. A number of large randomized control trials have evaluated crystalloid versus colloid as a resuscitation fluid in sepsis. No randomized trial or meta-analysis has demonstrated definitive benefit from using colloid for resuscitation [50–54]. Crystalloid is markedly cheaper, readily available, and should be used as the fluid of choice for resuscitation. If fluid resuscitation is inadequate to maintain minimal hemodynamic parameters, vasopressors should be started. Norepinephrine is the preferred first-line agent [49, 55]. Vasopressin can be added to norepinephrine if needed, and epinephrine and dopamine are alternative agents to norepinephrine [49]. In the setting of myocardial dysfunction suggested by low cardiac output or high cardiac filling pressures, dobutamine may be effective in maintaining adequate MAP [49].

Indicators of end-organ function such as mental status and urine output should be closely monitored to ensure adequate tissue perfusion. Tissue perfusion and correction of oxygen debt can also be measured by a number of laboratory endpoints including base deficit, lactate level, and mixed venous oxygen saturation (SVO<sub>2</sub>). Base deficit is the amount of base needed to titrate whole blood to a normal pH (7.4) at normal physiologic conditions, and because it is measured when PCO<sub>2</sub> is normal, it is a more specific marker of non-respiratory acid base disturbances than serum bicarbonate [56]. Increased base deficit correlates with amount of global tissue acidosis, resuscitation requirements, and mortality [57, 58]. Elevated lactate is a result of tissue dysoxia and has been used as an indirect measure of oxygen debt. Lactate accumulation in sepsis may not be the result of tissue oxygen deprivation and instead as a result of a hypermetabolic state with enhanced glycolysis and hyperlactatemia. It is therefore a less reliable indicator of oxygen debt, but decreasing levels of serum lactate may still be associated with improved outcomes [59, 60]. SVO<sub>2</sub> is dependent on cardiac output, oxygen demand, and hemoglobin and arterial oxygen saturation. A septic patient may have normal or elevated SVO<sub>2</sub> but not have adequate tissue oxygenation due to maldistribution of blood flow. Despite this, a low SVO<sub>2</sub> is an indicator of inadequate tissue oxygenation and requires quick intervention to increase oxygen delivery [61]. Using a resuscitation goal of SVO<sub>2</sub>  $> 65\%$  has been shown to improve outcomes [62].

None of these measured endpoints of tissue oxygenation are definitive on their own. They are single data points, which should be evaluated in combination with the clinical picture, hemodynamic measures, and end-organ function to guide resuscitation.

### 1.4.3 Antimicrobial Therapy

#### 1.4.3.1 Empiric Antibiotic Therapy

Source control is the cornerstone of treatment for IAIs; however, systemic antibiotic therapy is a critical adjunct. Uncomplicated IAIs are generally managed surgically and only require perioperative antibiotics. Complicated IAIs require early systemic antibiotic therapy to prevent bacteremia and spread of the infection and for the

reduction of late complications [63]. Timing to initiation of antibiotics is important and in cases of abdominal sepsis is critical and should occur within 1 h of diagnosis [49]. There are a number of standardized antibiotic regimens used in IAIs. The regimen used depends on the source of infection, patient's immune status, and likelihood of resistant organisms. Due to the variable pattern of flora in the gastrointestinal tract, the location of the perforated viscous will determine the offending organism. In a healthy individual, the stomach and duodenum are largely sterile or sparsely colonized with gram-positive organisms, lactobacilli, or *Candida*. Gram-negative organisms are found in the proximal small bowel and anaerobes in the distal small bowel and colon [8, 64]. If the source of IAI is known, location-specific organisms can be targeted. IAIs with unknown source should be treated with a broad-spectrum regimen based on patient risk factors. If there are no identifiable patient risk factors and the patient is deemed low risk, narrow-spectrum antibiotics can be started covering anaerobic and gram-negative organisms [8]. High-risk patients require broad-spectrum antibiotics covering for resistant organisms and tailored to the institution-specific antibiogram. Inadequate initial antibiotic treatment results in longer hospital stays, higher rates of postoperative abscesses and reoperation, and increased mortality [25, 65]. Cultures should be taken in high-risk patients so that antibiotics can then be de-escalated and tailored to the offending organism [66].

#### 1.4.3.2 Length of Treatment

Judicious and rational use of antimicrobials is a vital part of clinical practice in order to reduce the risk of antimicrobial resistance and worsening of emerging infections such as *Clostridium difficile*. For IAIs, timely empiric coverage with antimicrobials is critical for treatment, but mindfulness over length of treatment must also be considered. Previous practice involved continuing antibiotic therapy until resolution of fever, leukocytosis, and return of bowel function [67]. However, more recent studies have shown that a fixed shorter treatment course is adequate. Several recent studies have demonstrated that a 4-day course of antibiotics in conjunction with adequate source control had the same outcomes as longer courses of antibiotics in patients with complicated IAIs and abdominal sepsis [68, 69]. In fact, protracted antibiotic courses may be harmful. IAIs treated for greater than 7 days with antimicrobials were associated with increased extra-abdominal infections and mortality [70]. A recent task force termed AGORA (antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections) put forth a set of recommendations emphasizing early empiric treatment and the use of narrow-spectrum antimicrobials for community-acquired low-risk infections and broad-spectrum antimicrobials for hospital-acquired or high-risk infections. This task force also found that a treatment course as short as 4 days was sufficient for most patients with complicated IAIs when source control had been obtained [71]. Additionally, once tolerating oral intake, antimicrobials should be switched from intravenous to oral regimens and narrowed based on sensitivities from culture data [71]. Patients with signs of infection beyond 5–7 days of antibiotic treatment should undergo aggressive diagnostic maneuvers to identify ongoing uncontrolled sources of infection, antimicrobial treatment failure, or tertiary peritonitis [3].

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## Conclusion

Optimal care of IAI hinges on timely multifactorial care. Source control is the cornerstone of treatment and is tailored to the severity of the infection ranging from minimally invasive surgery or percutaneous drainage to a staged or damage control approach. Aggressive resuscitation and supportive care are paramount for physiologic recovery from the stress of the infection as well as the surgical intervention. Early, empiric antibiotic therapy based on patient risk stratification should be limited to a short fixed course unless the patient has poor clinical response in which case reassessment and possible re-intervention are indicated.

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# Inflammatory Mediators in Intra-abdominal Sepsis

# 2

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## 2.1 Abdominal Sepsis, Inflammatory Mediators, and Possible Therapeutic Strategies

The current consensus definitions for sepsis have defined sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection” [3, 4]. This new definition emphasizes the primacy of non-homeostatic host response to infection. Yet, at present, there is no gold-standard diagnostic test for this syndrome, mainly due to the current challenges in the microbiologic confirmation of infection. Thus, the clinical criteria of “suspected infection,” which include clinical signs and symptoms in a patient who requires antimicrobial treatment or body fluid culture, are suggested for operationalization proxies.

However, the clinical manifestations of sepsis are identical to those secondary to systemic inflammatory response syndrome (SIRS). The cause of SIRS can be infectious or noninfectious insults such as trauma, major surgery, acute pancreatitis, or

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